S/N 09/077,572 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael A. Apicella et al.	Examiner: S. Devi	
Serial No.:	09/077,572	Group Art Unit: 1645	
Filed:	October 13, 1998	Docket: 875.001US2	
Title:	NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA		

#34 Linda 4/24/04

DECLARATION OF CANDIS BUENDING

Commissioner for Patents
Washington, D.C. 20231

I, Candis Buending, state the following:

1. I am employed by Schwegman, Lundberg, Woessner & Kluth, P.A., Minneapolis, Minnesota, as a U.S. patent paralegal, and am paralegal for the attorney of record in this case, Ann S. Viksnins, Reg. No. 37, 748.

2. On August 17, 2001, Ms. Viksnins filed a Notice of Appeal and Petition for Extension of Time, with appropriate fees, and received a return receipt postcard with PTO date stamp of August 27, 2002 (copies enclosed).

3. On October 15, 2001, Ms. Viksnins filed an Appellants' Brief on Appeal, an Amendment and Response Under 37 CFR 1.116, and Request for Refund (copies enclosed), which were prepared for mailing by me.

4. On October 15, 2001, I signed the Certificate of Mailing under 1.8 on the above-noted documents and on a transmittal sheet; I placed these documents with a return postcard in an envelope addressed to: BOX AF, Commissioner of Patents, Washington, D. C. 20231; and on October 15, 2001, I deposited the envelope with the United States Postage Service with sufficient postage as first class mail.

5. The copies of documents being submitted to Examiner Devi herewith are true and correct copies of the documents originally mailed on October 15, 2001.

6. In response to Examiner Devi's telephone call to me on March 22, 2002, regarding this Appeal Brief, I made diligent inquiries within our office and with our docket clerks to determine whether the return receipt postcard date-stamped by the USPTO had been received, and was informed that it had not.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: March 22, 2002

Candis Buending

DELIVERED BY HAND

March 22, 2002

Examiner S. Devi
U.S. Patent and Trademark Office
Crystal Mall 1
Room 7E15
1911 South Clark Place
Alexandria, VA 22202

Re: Docket # 875.001US1
U.S. Patent Application SN 08/565,943:
NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA

Docket # 875.001US2
U.S. Patent Application SN 09/077,572
NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA

Dear Examiner Devi:

Received 26 Mar 02

In accordance with your request to me by telephone today, I enclose copies of the Notices of Appeal and Appeal Briefs with accompanying documents which we filed in these cases.

Since we have not to date received PTO return postcards for the briefs, for reasons which we assume relate to the post-September 11 delays at the PTO, I have included my Declaration with respect to the mailing of these briefs on October 15, 2001.

Please contact Ann Viksnins (612-373-6961) if you have any questions concerning these filings.

Sincerely yours,

Candy Buending
Paralegal to Ann S. Viksnins

CBB/Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Michael A. Apicella et al.

Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA

Docket No.: 875.001US2
Filed: October 13, 1998
Examiner: S. Devi
Serial No.: 09/077,572
Due Date: October 17, 2001
Group Art Unit: 1645

BOX AF
Commissioner for Patents
Washington, D.C. 20231

We are transmitting herewith the following attached items (as indicated with an "X"):

X A return postcard.
X Appellants' Brief on Appeal (5 pgs), with Appendices I-IV **(all in triplicate)**, with authorization to charge filing fee and oral hearing fee to Deposit Account No. 19-0743.
X Amendment & Response Under 3 CFR 1.116, including Clean Version of Substitute Paragraph of Specification and Clean Version of Pending Claims (10 pgs) **(in triplicate).**
X Request for Refund (2 pgs).

Please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional required fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938, Minneapolis, MN 55402 (612-373-6900)

By: _____
Atty: Ann S. Viksnins
Reg. No. 37,748

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: BOX AF, Commissioner for Patents, Washington, D.C. 20231, on this 15th day of October, 2001.

Candis B. Buending
Name

_____
Signature

Customer Number 21186
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A. P.O. Box 2938, Minneapolis, MN 55402
(612-373-6900)

(GENERAL)

In re Patent Application of: Michael A. Apicella et al.
Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA
Serial No.: 09/077,572 Filing Date: October 13, 1998
Receipt is hereby acknowledged for the following in the United States Patent and Trademark Office:

CONTENTS: Appellants' Brief on Appeal (5 pgs), with Appendices I-IV (all in triplicate); Amendment & Response Under 37 CFR 1.116, including Clean Version of Substitute Paragraph of Specification and Clean Version of Pending Claims (10 pgs; in triplicate); Request for Refund (2 pgs; in triplicate); a Return Postcard and TRANSMITTAL SHEET.

CHARGE TO DEPOSIT ACCT. 19-0743: BRIEF FILING FEE: $320.00 and ORAL HEARING FEE, $280.00

Mailed: October 15, 2001
ASV/cbb

Docket No.: 875.001US2
Due Date: October 17, 2001

In re Patent Application of: Michael A. Apicella et al.
Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA
Serial No.: 09/077,572 Filing Date: October 13, 1998

Receipt is hereby acknowledged for the following in the United States Patent and Trademark Office:

CONTENTS: Notice of Appeal (1 Page); check for fee of $310.00; a Return Postcard and TRANSMITTAL SHEET.

Mailed: August 17, 2001
ASV/cbb

Docket No.: 875.001US2
Due Date: August 21, 2001

In re Patent Application of: Michael A. Apicella et al.
Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA
Serial No.: 09/077,572 Filing Date: October 13, 1998

Receipt is hereby acknowledged for the following in the United States Patent and Trademark Office:

CONTENTS: An Amendment and Response Under 37 C.F.R. 1116 (10 Pages); a Copy of *Ex parte Parks*; a Return Postcard and TRANSMITTAL SHEET.

Mailed: March 16, 2001
ASV/cbb

Docket No.: 875.001US2
Due Date: April 21, 2001

S/N 09/077,572 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael A. Apicella et al.	Examiner: S. Devi	
Serial No.:	09/077,572	Group Art Unit: 1645	
Filed:	October 13, 1998	Docket: 875.001US2	
Title:	NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA		

NOTICE OF APPEAL FROM THE DECISION OF THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

BOX AF
Commissioner for Patents
Washington, D.C. 20231

In compliance with 37 C.F.R. § 1.191, Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated February 21, 2001, of the Examiner rejecting claims 22-26, 29, 32 and 33 of the above-identified patent application.

Our check in the amount of $310.00 is enclosed to pay the Notice of Appeal fee under 37 C.F.R. § 1.17(b).

We believe that no extension of time is necessary to respond to the Examiner's rejection, since Applicants filed their complete response within the two-month period from the date of mailing of the final Office Action. To date, Applicants have not received a further action from the Examiner, and are filing this Notice of Appeal to prevent possible abandonment.

If, in spite of the above explanation, a petition for extension and fees under 1.17(a) are deemed to be due, please consider this a request for extension, and charge any required fees to Deposit Account No. 19-0743.

Respectfully submitted,

MICHAEL A. APICELLA ET AL.

By Applicants' Attorneys,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6961

Date 17 August 2001 By _____
Ann S. Viksnins
Reg. No. 37,748

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to BOX AF, Commissioner of Patents, Washington, D.C. 20231 on August 17, 2001.

Candis B. Buending
Name

_____
Signature

In re Patent Application of: Michael A. Apicella et al.
Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA
Serial No.: 09/077,572 Filing Date: October 13, 1998

Receipt is hereby acknowledged for the following in the United States Patent and Trademark Office:

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Mailed: August 17, 2001
ASV/cbb

Docket No.: 875.001US2
Due Date: August 21, 2001

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#33
Linda
4/24/02

In re Application of:		)	
		)	
Michael A. Apicella et al.		)	Examiner: S. Devi
		)	
Serial No.:	09/077,572	)	Group Art Unit: 1645
		)	
Filed:	October 13, 1998	)	Docket: 875.001US2
		)	
For:	NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA	)	

APPELLANTS' BRIEF ON APPEAL

Box AF
Commissioner for Patents
Washington, D.C. 20231

Sir:

This Brief is presented in support of the Notice of Appeal mailed August 17, 2001 and filed in the U.S. Patent and Trademark Office on August 27, 2001, from the final rejection of claims 22-26, 29, 32 and 33 of the above-identified application, as set forth in the final Office Action mailed September 20, 2000. Appellants request an oral hearing.

This Brief is being submitted in triplicate, as set forth in 37 C.F.R. § 1.192(a).

A Petition for Extension of Time, with authorization to charge the fee to Deposit Account No. 19-0743, is enclosed.

The Commissioner is hereby authorized to charge the brief filing fee of $320.00 and request for oral hearing fee of $280.00, and any other fees which may be due, and to credit any overpayments, to Deposit Account No. 19-0743.

APPELLANTS' BRIEF ON APPEAL

TABLE OF CONTENTS

1. REAL PARTY IN INTEREST

The real party in interest of the above-captioned patent application is the assignee, University of Iowa Research Foundation.

2. RELATED APPEALS AND INTERFERENCES

The Appellants, their legal representatives, and the assignee are not aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF THE CLAIMS

For the purpose of this appeal, claims 22-26, 29, 32 and 33 stand rejected. Claims 22-26, 29, and 32-34 are the subject of this appeal (*see* Appendix I).

4. STATUS OF AMENDMENTS

Appellants on March 16, 2001 filed by facsimile a Response indicating the ATCC deposit numbers for nontypeable *Haemophilus influenza* strains 2019 B28 and 2019 B29. A copy of this document is enclosed in Appendix II. Appellants did not receive an Advisory Action with respect to this submission. Therefore, Appellants presume, for the purpose of this appeal, that this amendment was not entered.

Enclosed herewith is a Response amending the specification to indicate the ATCC deposit numbers for nontypeable *Haemophilus influenza* strains 2019 B28 and 2019 B29. The enclosed Response also provides amendments to claims 22 and 29, and newly added claim 34. Claims 24 and 26 have been amended to recite a mutant endotoxin that is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A. Claim 34 recites in dependent form an element of previously pending claim 22.

5. SUMMARY OF THE INVENTION

Gram-negative bacteria have an outer membrane comprised of proteins, lipoproteins, phospholipids, and glycolipids. The glycolipids comprise primarily endotoxin lipopolysaccharides (LPS) or lipooligosaccharides (LOS), depending on the genus of bacteria.. Specification at page 1, lines 21-26. LPS and LOS have potential as vaccines because of the antigenic determinants ("epitopes") residing in their carbohydrate structures. The chemical nature of LPS and LOS prevent the use of these molecules in vaccine formulations, because of the inherent toxicity of the lipid A portion. Accordingly, there are no currently available endotoxins that can safely be used as effective vaccines, *i.e.*, can induce an antibody response to these LPS or LOS antigenic epitopes. Specification at page 2, lines 21-35.

The present claims are directed to a method of making a mutant endotoxin, a mutant endotoxin made by this method, and a method of producing endotoxin-specific antisera, where the endotoxin has substantially reduced toxicity as compared to the wild-type endotoxin. Structurally, the endotoxin recited in the present claims is the same as the wild type endotoxin, except that it lacks at least one secondary acyl chain on lipid A.

6. ISSUE PRESENTED FOR REVIEW

1. Whether the specification provides adequate enablement under 35 U.S.C. § 112, first paragraph, for pending claims 22-26, 29 and 32-33.

7. GROUPING OF CLAIMS

The following grouping of claims is made in compliance with the requirements of 37 C.F.R. § 1.191 for the content of an Appeal Brief. The following grouping of claims is made to expedite this appeal and to narrow the issues, and is not intended to waive or limit the right of the Appellants to enforce and defend claims separately, even though they are grouped for convenience in this Appeal. For the purpose of this appeal all the pending claims (claims 22-26,

29 and 32-34) stand or fall together. All of the pending claims recite a mutant endotoxin, or make or use a mutant endotoxin, that (1) functionally has substantially reduced toxicity as compared to an endotoxin of a wild-type bacterial pathogen of the same species as the mutant pathogen, and (2) structurally is the same as wild type endotoxin except for lacking at least one secondary acyl chain on lipid A.

8. ARGUMENT

A. Applicable Law: 35 U.S.C. § 112, first paragraph

The first paragraph of 35 U.S.C. § 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 42 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1997).

1. Patent Office's Position

The Patent Office has taken the position that the specification fails to provide an enabling disclosure for the pending claims. The Patent Office acknowledges that Appellants have submitted a copy of the ATCC deposit receipt showing that the proper strains have been deposited under the provisions of the Budapest Treaty and provided the proper statement that all restrictions will be irrevocably removed upon the granting of a patent in compliance with 37 CFR 1.801-1.809. The Patent Office, however maintained the enablement rejection because Appellants in advertently provided the incorrect location in the specification into which the deposit information was to be inserted.

2. Appellants Response

Appellant encloses herewith a Response to the Office Action that indicates that the specification is to be amended at page 13 to recite that "Nontypeable *Haemophilus influenza* strains 2019 B28 and 2019 B29 were deposited on November 14, 2000 with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 under the provisions of the Budapest Treaty, and all restrictions will be irrevocably removed upon the granting of a patent on this application. Strain B28 has been accorded accession number PTA-2667 and strain B29 has been accorded accession number PTA-2668." Therefore, this rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

9. SUMMARY

Each of the pending claims subject to this appeal (claims 22-26, 29, 32-34) is patentable, and in particular, meets the requirements of 35 U.S.C. § 112, first paragraph). Reversal of the rejection and allowance of the claims is appropriate and is respectfully requested.

Respectfully submitted,

MICHAEL A. APICELLA ET AL.
By their Representatives,
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6961

Date 15 October 2001 By _____
Ann S. Viksnins
Reg. No. 37,748

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: BOX AF, Commissioner of Patents, Washington, D.C. 20231, on this 15th day of October, 2001.

Candis L. Prending
Name

_____
Signature

APPENDIX I

The Claims on Appeal

22. A method of making a mutant endotoxin comprising

mutating an *htrB* gene encoding a wild type endotoxin in a wild type gram-negative bacterial pathogen to provide the mutant endotoxin; wherein the mutant endotoxin is the same as the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A, and wherein the mutant endotoxin has substantially reduced toxicity when compared to the endotoxin of the wild type gram-negative bacterial pathogen.

23. A mutant endotoxin made according to the method of claim 22, wherein the mutant endotoxin was purified from the *htrB* mutant pathogen by phenol-water extraction or by protease digestion.

24. The mutant endotoxin according to claim 23, wherein the mutant endotoxin is conjugated to a carrier protein.

25. A mutant endotoxin made according to the method of claim 22.

26. The mutant endotoxin according to claim 25, wherein the mutant endotoxin is conjugated to a carrier protein.

29. A method for producing endotoxin-specific antisera, the method comprising

(a) immunizing an individual with a vaccine formulation comprising an *htrB* mutant of a gram-negative bacterial pathogen, endotoxin isolated from the *htrB* mutant of the gram-negative bacterial pathogen, or endotoxin purified from the *htrB* mutant of the gram-negative bacterial pathogen wherein the endotoxin is conjugated to a carrier protein; and

(b) collecting antibody produced from the immunized individual;

wherein the *htrB* mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A.

32. The method of claim 22 wherein the gram-negative bacterial pathogen is of the genera *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella* or *Pseudomonas*.

33. The method of claim 29 wherein the gram-negative bacterial pathogen is of the genera *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella* or *Pseudomonas*.

34. The method of claim 22, further comprising the step of purifying the mutant endotoxin.

APPENDIX II

Office Actions and Amendments

APPENDIX III

Art of Record and Other References

I. Art of Record

Karow *et al.*, *Journal of Bacteriology* 174:7407-7418 (1991)

Westphal *et al.*, *Methods Carbonydr. Chem.* 5:83-91 (1965)

JOURNAL OF BACTERIOLOGY, Nov. 1992, p. 7407–7418
0021-9193/92/227407-12$02.00/0

Vol. 174, No. 22

The Lethal Phenotype Caused by Null Mutations in the *Escherichia coli htrB* Gene Is Suppressed by Mutations in the *accBC* Operon, Encoding Two Subunits of Acetyl Coenzyme A Carboxylase

MARGARET KAROW,[1]† OLIVIER FAYET,[2] AND COSTA GEORGOPOULOS[1,3]*

Department of Cellular, Viral, and Molecular Biology, School of Medicine, University of Utah, Salt Lake City, Utah 84132[1]; Centre de Recherche de Biochimie et Genetique Cellulaires, Centre National de la Recherche Scientifique, F-31062 Toulouse Cedex, France[2]; and Biochimie Medicale, Centre Medical Universitaire, 1211 Geneva 4, Switzerland[3]

Received 17 July 1992/Accepted 18 September 1992

Insertion mutations in the *Escherichia coli htrB* gene result in the unique phenotype of not affecting growth at temperatures below 32.5°C but leading to a loss of viability at temperatures above this in rich media. When *htrB* bacteria growing in rich media were shifted to the nonpermissive temperature of 42°C, they continued to grow at a rate similar to that at 30°C but they produced phospholipids at the rate required for growth at 42°C. This led to the accumulation of more than twice as much phospholipid per milligram of protein compared with that in wild-type bacteria. Consistent with HtrB playing a role in phospholipid biosynthesis, one complementation group of spontaneously arising mutations that suppressed *htrB*-induced lethality were mapped to the *accBC* operon. This operon codes for the biotin carboxyl carrier protein and biotin carboxylase subunits of the acetyl coenzyme A carboxylase enzyme complex, which catalyzes the first step in fatty acid biosynthesis. Four suppressor mutations mapped to this operon. Two alleles were identified as mutations in the *accC* gene, the third allele was identified as a mutation in the *accB* gene, and the fourth allele was shown to be an insertion of an IS*1* transposable element in the promoter region of the operon, resulting in reduced transcription. The suppressor mutations caused a decrease in the rate of phospholipid biosynthesis, restoring the balance between the biosynthesis of phospholipids and growth rate, thus enabling *htrB* bacteria to grow at high temperatures.

During a screen for new *Escherichia coli* heat shock genes, two insertion mutations in the *htrB* gene were isolated. Bacteria carrying either of these two mutations grow in a completely wild-type manner at temperatures below 32.5°C but are inviable at higher temperatures in rich media (23). Although *htrB* was later shown not to be a heat shock gene (24), its unique temperature requirement is intriguing because, for the most part, *E. coli* cells growing between 21 and 37°C show very few temperature-dependent adaptive responses (20). One of the changes that occurs is an alteration in the composition of lipids that is required for the maintenance of membrane fluidity (30). Originally, we disregarded the possibility that HtrB may directly affect membrane structure because known mutants unable to correctly alter their lipid composition are viable at all temperatures (9, 40). Rather, on the basis of the similarity of the morphology of *htrB* bacteria grown at nonpermissive temperatures to that of cell wall biosynthesis mutants (5), we proposed that HtrB was involved in cell wall biosynthesis (23). However, further studies have led us to conclude that HtrB most likely does play a role in membrane structure.

This conclusion originated from the study of a multicopy suppressor of *htrB*, *msbB*. These multicopy suppressors are genes that when cloned onto multicopy plasmids rescue the Ts⁻ phenotype of *htrB*. The protein encoded by *msbB* may serve a role similar to that of HtrB, since the MsbB protein sequence is similar to that of HtrB (25). In addition, null mutations in either the *msbB* or *htrB* gene result in a similar and unique phenotype, namely, the ability to grow on fourfold higher concentrations of deoxycholate than can wild-type bacteria (25). The increased resistance to deoxycholate most likely indicates that *htrB* and *msbB* bacteria have alterations affecting membrane structure, possibly the lipopolysaccharide (LPS) layer.

In general, mutations that affect the LPS layer alter the resistance of bacteria to hydrophobic compounds. Although most known LPS mutants are hypersensitive to hydrophobic molecules (35), there are a few mutants which exhibit increased resistance to hydrophobic molecules. The best studied of these is a mutant of *Salmonella typhimurium*, the *pmrA* mutant (41). This mutant exhibits an increased resistance to the hydrophobic drug polymyxin B. The increased resistance has been shown to be associated with a decrease in the positive charge of a portion of the LPS molecules, thus reducing the number of binding sites for the negatively charged polymyxin B (42). A similar type of change in LPS structure may lead to the increased resistance to deoxycholate of *htrB* and *msbB* bacteria. For example, a decrease in the amount of LPS molecules with negatively charged phosphoethanolamine residues could lead to fewer binding sites for the positively charged deoxycholate molecules.

Another indication that HtrB affects the membrane structure is that low levels of cationic detergents suppress its Ts⁻ phenotype (25). The cationic detergents may act by altering the interactions between the LPS molecules and divalent cations or polyamines. The addition of Ca^{2+} or Mg^{2+}

* Corresponding author.
† Present address: Department of Microbiology and Immunology, Temple University Health Sciences Center, Philadelphia, PA 19140.

TABLE 1. Strains

Strain	Relevant characteristic(s)	Reference or source
W3110	Wild type	Our collection
B178	W3110 *galE*	14
MLK53	W3110 *htrB1*::Tn*10*	23
MLK777	B178 *htrB1*::Tn*10* *zhb-43*::Tn*10*-Kan^r	This work
MLK993	MLK53 Ts$^+$1031 *zhb-43*::Tn*10*-Kan^r	This work
MLK1000	MLK53 Ts$^+$1123 *zhb-43*::Tn*10*-Kan^r	This work
MLK995	MLK53 Ts$^+$1043-1 *zhb-43*::Tn*10*-Kan^r	This work
MLK994	MLK53 Ts$^+$1043-6 *zhb-43*::Tn*10*-Kan^r	This work
MLK519	B178 *htrB1*::Tn*10* Ts$^+$1031(λ)	This work
MLK1067	W3110 *msbB*::Ωcam	25
MLK986	MLK53 *msbB*::Ωcam	25
MLK1086	MLK986 Ts$^+$1043-1 *zhb-43*::Tn*10*-Kan^r	This work
MLK1087	MLK986 Ts$^+$1043-6 *zhb-43*::Tn*10*-Kan^r	This work
DH5α	*recA1*	Bethesda Research Laboratories

reverses this rescue, possibly by competing for the same sites on the LPS molecules (25). These results have led us to propose that HtrB affects outer membrane structure and function (25).

In an attempt to further understand the role of HtrB in bacterial physiology, we have undertaken the study of a second type of *htrB* suppressor: single-copy, spontaneously arising, extragenic suppressor mutations. Presumably, these mutations directly or indirectly alter functions that are affected by the lack of HtrB. By mapping these suppressor mutations and identifying the genes that encode them, we hoped to clarify the role that HtrB plays in *E. coli* physiology. Consistent with the proposal that HtrB plays a role in membrane structure and function, we report here that one complementation group of such suppressors affects the biosynthesis of phospholipids and that HtrB may play a role in the coupling of phospholipid biosynthesis and growth rate.

MATERIALS AND METHODS

Bacterial strains and media. The bacterial strains used in this study are shown in Table 1. Early work with the suppressor mutations was done in the B178 background. B178 carries a *galE* mutation which blocks the mucoidy associated with wild-type bacteria (14). After the discovery that HtrB itself may affect membrane function, all mutations were moved into the wild-type W3110 background. All experiments presented here were performed using this background strain, unless otherwise indicated. Bacteria were grown in Luria-Bertani (LB) medium prepared as described previously (23). L agar is LB medium with 1% agar. Antibiotics were added when needed, at the following final concentrations: ampicillin, 50 μg/ml; spectinomycin, 50 μg/ml; tetracycline, 10 μg/ml; chloramphenicol, 12 μg/ml; and kanamycin, 50 μg/ml.

Cell growth analysis. Bacterial growth, viability experiments, and photography were performed as described previously (23).

Plasmids. The pKS-1031 and pKS-1031-2 plasmids carry the 6-kb *Bam*HI fragment of λ transducing phage 6G3 (λS29) from the library made by Kohara et al. (26), cloned in both orientations into the *Bam*HI site of the pBluescript-KS plasmid (Stratagene). In pKS-1031, the fragment is oriented such that the T7 promoter on the plasmid is located 5′ to all of the open reading frames encoded on the fragment. The pBK2 plasmid was made by partially digesting pKS-1031 with *Kpn*I, digesting it to completion with *Bam*HI, isolating the 4-kb fragment from a low-melting-point agarose gel (FMC), and ligating the fragment to *Bam*HI-*Kpn*I-digested pBluescript-SK plasmid DNA. The p3/49 and p3/58 plasmids and the p2/53 plasmid are deletion derivatives of pKS-1031 and pKS-1031-2, respectively. These deletions were made according to the DNase I method of Hong (19). After partial DNase I digestion, the DNA was digested with *Eco*RI, ligated, and digested with *Pst*I to enrich for plasmids with deletions. The pE1 and pEK plasmids are the 900-bp *Eco*RV and *Eco*RV-*Kpn*I fragments of pKS-1031 cloned into the *Eco*RV and *Eco*RV-*Kpn*I sites of pBluescript-KS, respectively. The pGB-*accB* plasmid is the 2.3-kb *Eco*RV fragment from pKS-1031 cloned into the *Sma*I site of pGB2 (8). The pLac-*accC* plasmid was made by first digesting pKS-1031 with *Kpn*I and then partially digesting it with *Eco*RV. The 1.85-kb fragment was isolated from low-melting-point agarose and ligated with *Eco*RV- and *Kpn*I-digested pBluescript-KS plasmid DNA.

Genetic manipulations. P1-mediated transductions were performed as described by Miller (31).

Isolation of mini-Tn*10*-Kan^r elements linked to the cold-sensitive (Cs$^-$) suppressor mutations was accomplished by P1 transduction of a library of mini-Tn*10*-Kan^r insertions (45) into the suppressor strains, selecting simultaneously for Kan^r and colony formation at 30°C. The Cs$^+$ Kan^r colonies were then restreaked at 30 and 42°C. Normal growth at 30°C but inviability at 42°C indicated that the wild-type copy of the suppressor mutation was cotransduced with the mini-Tn*10*-Kan^r marker.

To determine complementation of the Ts$^+$1031 Cs$^-$ phenotype with the Kohara et al. λ clones (26), an aliquot of each clone was used to infect a fresh culture of *htrB* Ts$^+$1031(λ) (MLK519) and the bacteria were plated at 30°C. Colonies that grew were restreaked at 30 and 42°C to identify which phage clones complemented the growth defect.

Cloning and mapping of the *zhb-43*::Tn*10*-Kan^r marker. The *zhb-43*::Tn*10*-Kan^r marker was transduced into strain CG1151 (MC1040-2 carrying the Cam^R vector Mu dS005 [15]). A library of mini-Mu clones was made as described by Groisman and Casadaban (15) and plated on W3110(Mu) (MLK47). Clones which carry the mini-Tn*10*-Kan^r marker were isolated by selecting simultaneously for Kan^r and Cam^r, and one of them was used to probe the Kohara library of λ clones (26) by the techniques previously described (23).

PCR. Polymerase chain reactions (PCRs) were carried out by the method of Innis and Gelfand (21). The two primers used to amplify the coding region of *accB* were 5′-GCAATC

TCGCCGCCGGTTGGC-3' and 5'-GAACGGTCGCCGGAGCGGCT-3'. The primers used to amplify the promoter region of the *accBC* operon were 5'-CGACCTCGTCCTCCCTGACG-3' and 5'-GAACGGTCGCCGGAGCGGCT-3'.

DNA sequencing. Sequencing was done with Sequenase (version 2.1) as described by the manufacturer (United States Biochemical). PCR products were sequenced by the snap-cooling method of Kusukawa et al. (28). The 5'-CGACCTCGTCCTCCCTGACG-3' primer, used to make the PCR products, was also used to sequence across one IS*1* junction. The other junction was sequenced with a primer homologous to the IS*1* element, 5'-CCATCATACACT AAATCAG-3'.

Northern blot analysis. Isolation of RNA and Northern (RNA) blot analysis were performed as described previously (24). The *accBC* probe was the *Hin*dIII-*Pst*I DNA fragment internal to *accBC* and was labeled as described previously (24). To control for even loading of the RNA samples, the blot was stained with methylene blue after the hybridization procedure (18).

Western blot analysis. Western blots (immunoblots) were carried out as described by Ang and Georgopoulos (3). Streptavidin conjugated with alkaline phosphatase (Bethesda Research Laboratories) was used to detect the biotinylated BCCP with the chemiluminescence detection kit Western-light, from Tropix.

Fatty acid analysis. Bacterial cultures were first grown at their permissive temperatures to mid-log phase in LB medium, diluted into 50 or 100 ml of the same medium to an optical density at 595 nm (OD_{595}) of 0.05, and grown at 30 or 42°C to an OD_{595} of 0.4. The bacteria were harvested by centrifugation, and after the bacteria were washed twice with 10 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES) (pH 7.9) or 10 mM $MgCl_2$, fatty acids were extracted by the method of Bligh and Dyer (6) as described by Ames (2). The phospholipid fraction was isolated by direct extraction of the washed bacteria. The LPS-enriched fraction was isolated from the monophase of this extraction, present in the insoluble pellet, as described by Galloway and Raetz (12). The pellet was hydrolyzed in 6 N HCl for 3 h at 100°C, and fatty acids were extracted by the method of Bligh and Dyer (6). Methyl esters of the fatty acids were made with BF_3 and analyzed by gas chromatography on Supelco SPB-1 fused silica (15 m by 0.25 mm with 1-μm film thickness), with helium as the carrier gas (10 lb/in^2) and a temperature program of 5°C/min, 150 to 250°C. Supelco bacterial fatty acid methyl ester CP mixture 4-7080 was used to determine retention times of the individual fatty acids.

Quantification of esterified fatty acids. Bacterial cultures were grown as described for fatty acid analysis. After pelleting by centrifugation, the bacteria were washed once with 10 mM $MgCl_2$, and the phospholipids were isolated by the method of Bligh and Dyer (6). Following lyophilization, the lipids were quantitated as hydroxamates by the method of Stern and Shapiro (38). Standard curves were obtained with L-α-phosphatidylcholine di-heptadecanoyl (Sigma). All phospholipid quantities are given using an average molecular weight of 700.

Quantification of 3-deoxy-D-manno-octulosonic acid. Bacterial cultures of 400 ml were grown as described for fatty acid analysis. After the bacteria were washed once with ice-cold 50 mM Tris (pH 7.9) and resuspended in the same buffer, they were passed twice through a French press. The suspension was centrifuged at 5,000 × *g* for 5 min to remove large debris, and the supernatant was centrifuged at 30,000 × *g* for 60 min at 4°C. The resulting pellet was used as the outer membrane fraction and was washed once with 50 [illegible] (pH 7.9) and once with 10 mM HEPES (pH 7.4) before [illegible]. The remaining supernatant was centrifuged for 90 [illegible] 175,000 × *g* at 4°C. The resulting pellet was used [illegible] membrane fraction and was washed as described [illegible]. The inner and outer membrane fractions were resuspended in 50 μl of distilled H_2O and assayed for protein as described below and for 3-deoxy-D-manno-octulosonic acid by the method of Weissbach and Hurwitz (46). LPS purchased from Sigma was used as the standard.

Protein determination. Following the washing procedures described above, a portion of each culture was lysed in 0.5% sodium dodecyl sulfate–10 mM EDTA–10 mM Tris (pH 7.9) at room temperature or at 55°C for highly concentrated suspensions of bacteria. Protein concentrations were determined with the bicinchoninic acid protein assay reagent purchased from Pierce, with bovine serum albumin as the standard.

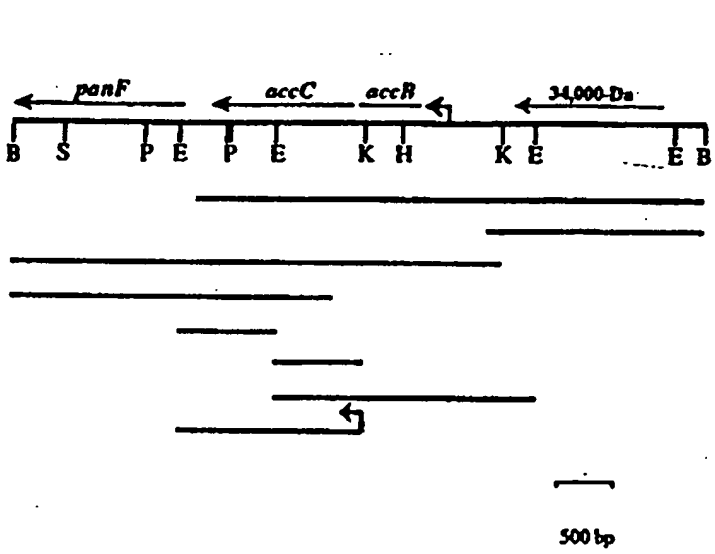
Determination of phospholipid biosynthesis rates. Bacteria were grown at their permissive temperatures to mid-log phase in LB medium and diluted to an OD_{595} equal to 0.05. 10 μCi of [1-^{14}C]acetate (NEN-Dupont) was added, and the 1-ml cultures were shifted to 42°C at time zero. Aliquots were taken at the appropriate times, and the phospholipids were extracted by the method of Bligh and Dyer (6). The chloroform-solubilized phospholipids were washed twice with 2 M KCl and once with distilled H_2O before scintillation counting.

RESULTS

Identification and cloning of the wild-type copies of the suppressor genes. Extragenic suppressors of the *htrB* insertion mutations arise spontaneously at a frequency of approximately 10^{-4} at the nonpermissive temperature of 42°C. Approximately one-third of these suppressor mutations show, to various degrees, a Cs$^-$ phenotype (i.e., slow or no growth at 30°C or below). Using this Cs$^-$ phenotype, complementation analysis with linked mini-Tn*10*-Kan^r markers (45) was performed to assign these suppressor mutations into several different complementation groups (data not shown). One of these classes consisted of two alleles, Ts$^+$1123 and Ts$^+$1031, that were extremely cold sensitive, being unable to form colonies at 30°C or below. Because of the tight Cs$^-$ phenotype of these two mutations, we were able to clone their corresponding wild-type genes by complementation.

The cloning of the wild-type genes in which the Ts$^+$1123 and Ts$^+$1031 mutations were located was done by first localizing a closely linked mini-Tn*10*-Kan^r element, *zhb-43*::Tn*10*-Kan^r. This was accomplished by cloning the *zhb-43*::Tn*10*-Kan^r marker into a mini-Mu plasmid (described in Materials and Methods) and using [α-^{32}P]dATP-labeled plasmid DNA to probe the overlapping λ clones of the *E. coli* genomic library made by Kohara et al. (26). The *zhb-43*::Tn*10*-Kan^r mini-Mu plasmid DNA hybridized to phage clones 6G3, 6G9, and 3C5 (λ529 to λ531), corresponding to the 71-min region on the *E. coli* chromosome. To identify the phage(s) that carries the intact wild-type gene, we infected *htrB* Ts$^+$1031(λ) (MLK519) bacteria with phage clones 3G10 to 4G11 (λ523 to λ535), covering a total of 70 kb of DNA on each side of the *zhb-43*::Tn*10*-Kan^r marker. Among those recombinant phages tested, only 2ID3 and 6G3 (λ528 and λ529) complemented the Cs$^-$ phenotype of the Ts$^+$1031 mutation.

We further localized the complementation activity to a *Bam*HI fragment of approximately 6 kb that was isolated



	Complementation of suppressor mutation	
	Ts+ 1031	Ts+ 1123
pKS-1031	+	+
p3/58	+	+
p3/49	-	-
pBK2	+	+
p2/53	-	MR
pE1	-	MR
pEK	-	-
pGB-*accB*	MR	-
pLac-*accC*	-	+

FIG. 1. Restriction map of the pKS-1031 plasmid and complementation of the suppressor mutations. The directions of transcription and open reading frames of the four genes encoded on pKS-1031 are indicated above the restriction map. Restriction sites are marked with abbreviated forms of the names of the restriction endonucleases: B, *Bam*HI; S, *Sal*I; P, *Pst*I; E, *Eco*RV; K, *Kpn*I; H, *Hin*dIII. Deletion derivatives and subclones are shown below the restriction map, the bars indicate the portion of pKS-1031 that is cloned in each case, and the name of each clone is shown to the right along with its ability to complement. The arrow above the pLac-*accC* clone represents the *lacIQ* promoter encoded on the vector. Complementation of the suppressor mutations is indicated with a plus symbol, marker rescue of the mutation is indicated as MR, and noncomplementing clones are indicated with a minus symbol.

from λ6G3 and cloned into pBluescript-KS (pKS-1031). A combination of methods, including partial DNA sequencing, analysis of the proteins encoded on this fragment with the T7 polymerase-promoter system of Tabor and Richardson (39), and comparison of the restriction map of pKS-1031 to the published restriction maps of this region (1, 22, 29, 34, 43) (data not shown), identified this 6-kb clone as carrying the genes coding for pantothenate permease (*panF*), BCCP (*accB*), biotin carboxylase (*accC*), and a 34,000-Da protein of unknown function. Figure 1 shows the arrangement of these genes on this 6-kb fragment.

A set of deletion derivatives and subclones of this fragment were made to determine which of these genes was required for complementation of the Cs$^-$ phenotype of the Ts$^+$1031 and Ts$^+$1123 mutations. It was found that only deletion derivatives p3/58 and pBK2 were able to complement (Fig. 1). The *accBC* genes, coding for BCCP and biotin carboxylase, are the only genes common to both of these derivatives. These two genes have recently been shown to form an operon, with the promoter located 5′ to the *accB* gene (29) (Fig. 1).

Isolation of non-cold-sensitive suppressor alleles. To determine whether the extreme Cs$^-$ phenotype was invariably linked with the ability of these mutations to suppress *htrB*, we isolated new alleles without prior screening for a Cs$^-$ phenotype. To do this we transduced the *zhb-43*::Tn*10*-Kan^r marker into *htrB* mutant bacteria, and three independent isolates were grown overnight in liquid at 42°C to allow suppressor mutations to accumulate. The *zhb-43*::Tn*10*-Kan^r marker and any suppressor mutations linked to it were transduced back into *htrB* bacteria and identified by selecting simultaneously for Kan^r and colony formation at 42°C. Only one Ts$^+$ suppressor isolate from each of the three original cultures was characterized to ensure that each new suppressor was due to an independent mutational event. Two of three such suppressor mutations, Ts$^+$1043-1 and Ts$^+$1043-6, were shown to be linked to the *zhb-43*::Tn*10*-Kan^r marker by transduction, and both were mapped to the *accBC* operon by complementation studies (Fig. 1). Since both of these new suppressor strains formed colonies at 30°C, it appears that the extreme Cs$^-$ phenotype is not a prerequisite for suppression. However, both mutations affected bacterial growth at 30°C (Fig. 2A); *htrB* Ts$^+$1043-6 bacteria grew slightly more slowly than the wild type, and *htrB* Ts$^+$1043-1 bacteria grew more slowly still, with a rate approaching that of *htrB* Ts$^+$1123 bacteria, which did not form colonies at 30°C.

Suppression of the HtrB phenotypes. All four of the suppressor mutations restored the ability of *htrB* bacteria to grow at 42°C, albeit at a lower growth rate than that of wild-type bacteria (Fig. 2B). The altered morphology that accompanies the loss of viability of *htrB* bacteria was also suppressed in these strains. Photographs of isogenic wild-type bacteria, *htrB* mutant bacteria, and *htrB* Ts$^+$1043-6 bacteria are shown in Fig. 2C. The *htrB* bacteria formed their characteristic bulges, whereas *htrB* bacteria with the Ts$^+$1043-6 suppressor mutation exhibited a wild-type morphology. Although the suppressor mutations suppressed the lethal phenotype caused by *htrB*, they did not suppress the increased deoxycholate resistance exhibited by *htrB* bacteria at 30°C. Whereas the MIC of deoxycholate for wild-type bacteria was 2.5%, both *htrB* and the suppressor strains grew on L agar supplemented with 10% deoxycholate (data not shown).

To further pursue the question of which of the HtrB phenotypes were reversed by the suppressor mutations, we checked their effects on *htrB msbB* double-mutant bacteria. The *msbB* gene was originally isolated as a multicopy suppressor of *htrB* and subsequently shown to code for

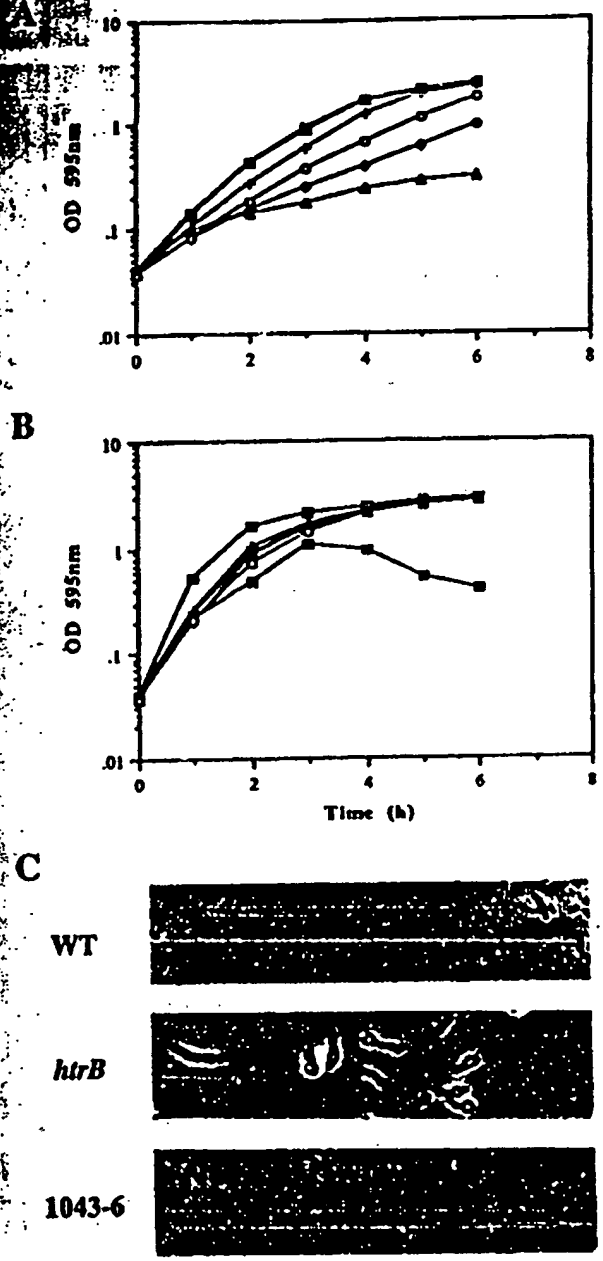


FIG. 2. Morphology and growth curves of wild-type, *htrB*, and various suppressor derivative bacteria. (A and B) Growth curves at 30°C (A) and 42°C (B) of isogenic wild-type (□), *htrB* (■), *htrB* Ts⁺1031 (△), *htrB* Ts⁺1123 (◇), *htrB* Ts⁺1043-1 (○), and *htrB* Ts⁺1043-6 (+) bacteria. (C) Photographs of wild-type (WT), *htrB*, and *htrB* Ts⁺1043-6 (1043-6) bacteria grown at 42°C from an OD_{595} of 0.05 for 2.75 h.

protein similar to HtrB (25). We previously concluded that MsbB plays a role similar to and possibly redundant with that of HtrB because *htrB msbB* double-mutant bacteria exhibit phenotypes at 30°C that are not associated with either of the single mutations, including a heterogeneous alteration in morphology (i.e., filamentous and fat, tadpole-shapen cells) and a growth rate that is lower than that of wild-type bacteria (25). The presence of the Ts⁺1043-1 or Ts⁺1043-6 mutation suppressed the morphological alterations of the *htrB msbB* bacteria, but the slow-growth phenotype was actually accentuated in the triple mutants (data not shown).

Molecular analysis of the suppressor mutations. To identify which of the two genes in the *accBC* operon were mutated in these suppressor strains, we cloned the two wild-type genes individually on separate plasmids and used them to map the location of the four suppressor mutations. The *accB* gene, coding for BCCP, was subcloned into the low-copy-number vector pGB2 (8) on a 2.3-kb *Eco*RV fragment (pGB-*accB*). This fragment was cloned into a low-copy-number vector because its cloning, or the cloning of any fragment carrying the *accB* gene alone, onto higher-copy-number vectors has been unsuccessful thus far. The biotin carboxylase gene, *accC*, was cloned onto a 1.85-kb *Kpn*I-*Eco*RV fragment under the control of the *lac* promoter of pBluescript-KS (pLac-*accC*). Figure 1 shows the relationship of these subclones to the full-length pKS-1031 clone and the locations of the coding regions for BCCP and biotin carboxylase.

When either pLac-*accC* or pGB-*accB* was transformed into *htrB* bacteria, the bacteria formed colonies at 42°C. This finding was surprising, since the pKS-1031 plasmid containing the entire *accBC* operon did not rescue *htrB* bacterial growth at 42°C (data not shown). This ability to rescue appears to be the result of a stoichiometric imbalance of these two enzyme subunits, altering the activity of the acetyl coenzyme A (acetyl-CoA) carboxylase enzyme complex in a manner analogous to that caused by the suppressor mutations themselves (see below).

Complementation of the Cs⁻ phenotype of the Ts⁺1031 and Ts⁺1123 mutations by pLac-*accC* and pGB-*accB* was determined by colony formation at 30°C. The pLac-*accC* plasmid complemented the Cs⁻ phenotype of the Ts⁺1123 mutation, indicating that this mutation mapped to the *accC* gene. We further localized Ts⁺1123, by marker rescue, to the 950-bp *Eco*RV fragment (pE1) in the region encoding the carboxy terminus of the biotin carboxylase protein (Fig. 1). The Cs⁻ phenotype of the Ts⁺1031 mutation was not complemented by either of the subclones, despite the fact that it was complemented by the full-length pKS-1031 plasmid (Fig. 1). However, the pGB-*accB* plasmid rescued *htrB* Ts⁺1031 mutant bacteria by recombination, indicating that the Ts⁺1031 mutation was located within this fragment. The inability of both pLac-*accC* and pGB-*accB* to complement the Cs⁻ phenotype of Ts⁺1031 could indicate that this mutation exerts a polar effect on the expression of the *accB* gene or affects the promoter region of the *accBC* operon. To differentiate between these two possibilities, this mutation was characterized further, as described below.

Because the Ts⁺1043-1 and Ts⁺1043-6 suppressor mutations did not exhibit an extreme Cs⁻ phenotype, one way to map them would have been to assess complementation by the reappearance of the Ts⁻ phenotype of *htrB*. However, the above-mentioned ability of either pLac-*accC* or pGB-*accB* to rescue *htrB* at 42°C made this strategy impossible. Fortuitously, the presence of either pLac-*accC* or pGB-*accB* did not fully reverse the morphological alterations exhibited by *htrB msbB* double-mutant bacteria, so this double-mutant background was used to map the Ts⁺1043-1 and Ts⁺1043-6 mutations. When *htrB msbB* Ts⁺1043-6 triple-mutant bacteria were transformed with the pLac-*accC* plasmid, the

resulting bacterial morphology was identical to that exhibited by the unsuppressed *htrB msbB* double mutant, indicating that Ts⁺1043-6 most likely was a mutation in the *accC* gene (Fig. 1). The opposite result was obtained with the *htrB msbB* Ts⁺1043-1 triple-mutant bacteria. The presence of the pGB-*accB* plasmid resulted in the appearance of filamentous cells, a phenotype exhibited by *htrB msbB* double-mutant bacteria carrying pGB-*accB*, indicating that Ts⁺1043-1 was most likely a mutation in the *accB* gene (Fig. 1).

Analysis of the Ts⁺1031 mutation. To determine whether the Ts⁺1031 mutation was a polar mutation in the *accB* gene or a promoter mutation, we used PCR to amplify the *accB* gene from genomic DNA isolated either from bacteria carrying the Ts⁺1031 mutation or from the isogenic wild-type strain. We first amplified and sequenced the coding region of the *accB* gene and found that there were no changes in the Ts⁺1031 DNA sequence. We then amplified the promoter region of the operon and found that the PCR product made from the DNA of the Ts⁺1031 mutant was approximately 750 bp longer than the corresponding PCR product made from wild-type DNA (data not shown). The sequencing of this PCR fragment showed that there was an IS*1* element inserted 215 bp upstream of the translational start codon for BCCP. Li and Cronan (29) have recently located the transcriptional start site of the *accBC* operon to 296 bp upstream of the *accB* coding region. Thus, the Ts⁺1031 mutation was an IS*1* element inserted within this unusually long, 5′-untranslated leader region (Fig. 3A). The *accBC* promoter has previously been shown to be located in a region of bent DNA (27, 29, 32, 34); the IS*1* element has inserted at one end of this bent DNA region. Like most IS*1* insertion events (11), a 9-bp direct repeat was created in the *accBC* DNA (Fig. 3A).

IS*1* elements have been shown to exert polar effects on transcription, as well as create new promoters at their site of insertion (11). These promoters are created by fusing a preexisting −35 promoter recognition sequence, within the IS*1* element, to potential −10 promoter recognition sequences in the genome. In this case it is likely that transcription from the *accBC* promoter terminated within the element and that the small quantity of residual transcription seen was due to initiation at a newly created promoter, much weaker than the *accBC* promoter, as illustrated in Fig. 3A. The activity of this promoter was low probably because the spacing between the putative −10 and −35 regions is 6 bp shorter than the average spacing between −10 and −35 regions (33).

Northern blot analysis was performed to determine the effect of the IS*1* element insertion on the transcription of the operon. To determine whether any of the other suppressor mutations affect the expression of the operon, we included RNA from the other suppressor strains, as well as *htrB* and wild-type bacteria, grown at either 30 or 42°C. As shown in Fig. 3B, only the Ts⁺1031 mutation had a substantial effect on *accBC* expression; the insertion of the IS*1* element was found to greatly reduce the transcription of this operon at both 30 and 42°C.

One would expect that such a large decrease in the amount of mRNA would be reflected by the amount of BCCP and biotin carboxylase protein present in the cell. Using streptavidin conjugated to alkaline phosphatase and a chemiluminescent substrate, biotinylated BCCP was detected on Western blots. As shown in Fig. 3C, the quantity of biotinylated BCCP was indeed reduced at 30°C, but surprisingly, at 42°C the reduction was not as much as would be expected considering the results obtained from the Northern blot experiment.

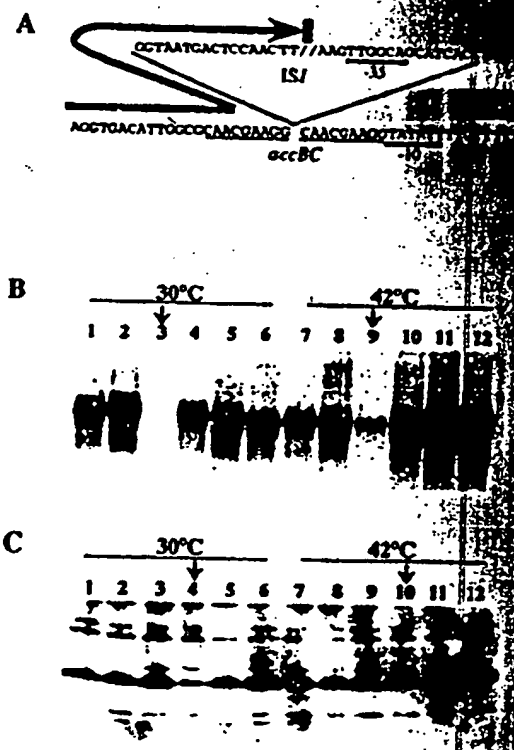


FIG. 3. Effects of the IS*1* transposable element insertion mutation, Ts⁺1031, on the expression of the *accBC* operon. (A) Model of the mechanism by which the insertion of the IS*1* element decreases the transcription of the *accBC* operon. The IS*1* element is indicated above the *accBC* DNA sequence, and the exact point of insertion in the *accBC* DNA is indicated by a gap in the sequence. The boldface arrow, initiating from the left, represents transcription from the *accBC* promoter. The bar at which this arrow ends indicates transcriptional termination within the IS*1* element. Potential −35 and −10 RNA polymerase recognition signals are marked. Thin lines below the *accBC* sequence indicate the 9-bp repeat created by the insertion of the IS*1* element. The small arrow to the right, above the *accBC* DNA sequence, represents the lower level of transcription initiated at this putative new promoter. (B) Northern blot of RNA isolated from wild-type (lanes 1 and 7), *htrB* (lanes 2 and 8), *htrB* Ts⁺1031 (lanes 3 and 9), *htrB* Ts⁺1123 (lanes 4 and 10), *htrB* Ts⁺1043-1 (lanes 5 and 11), and *htrB* Ts⁺1043-6 (lanes 6 and 12) bacteria grown at 30 or 42°C. (C) Western blot analysis of biotinylated BCCP protein from wild-type (lanes 1 and 7), *htrB* (lanes 2 and 8), *htrB* Ts⁺1123 (lanes 3 and 9), *htrB* Ts⁺1031 (lanes 4 and 10), *htrB* Ts⁺1043-1 (lanes 5 and 11), and *htrB* Ts⁺1043-6 (lanes 6 and 12) bacteria grown at 30 or 42°C. The arrows above the lanes serve to highlight the *htrB* Ts⁺1031 results. The bar to the right of the Western blot indicates the position of the BCCP protein.

Fatty acid analysis of *htrB* and the suppressor mutations. The only other known mutation of the *accBC* operon is *fabE* (16). This mutation results in a Ts⁻ phenotype and has recently been shown to be a point mutation in the *accB* gene near the region encoding the biotin attachment site of BCCP (29). When *fabE* or *fabD* Ts⁻ mutants (FabD catalyzes the second step in fatty acid biosynthesis) are grown at semipermissive temperatures, their fatty acid compositions are altered (16, 17). This alteration reflects the use of most of the

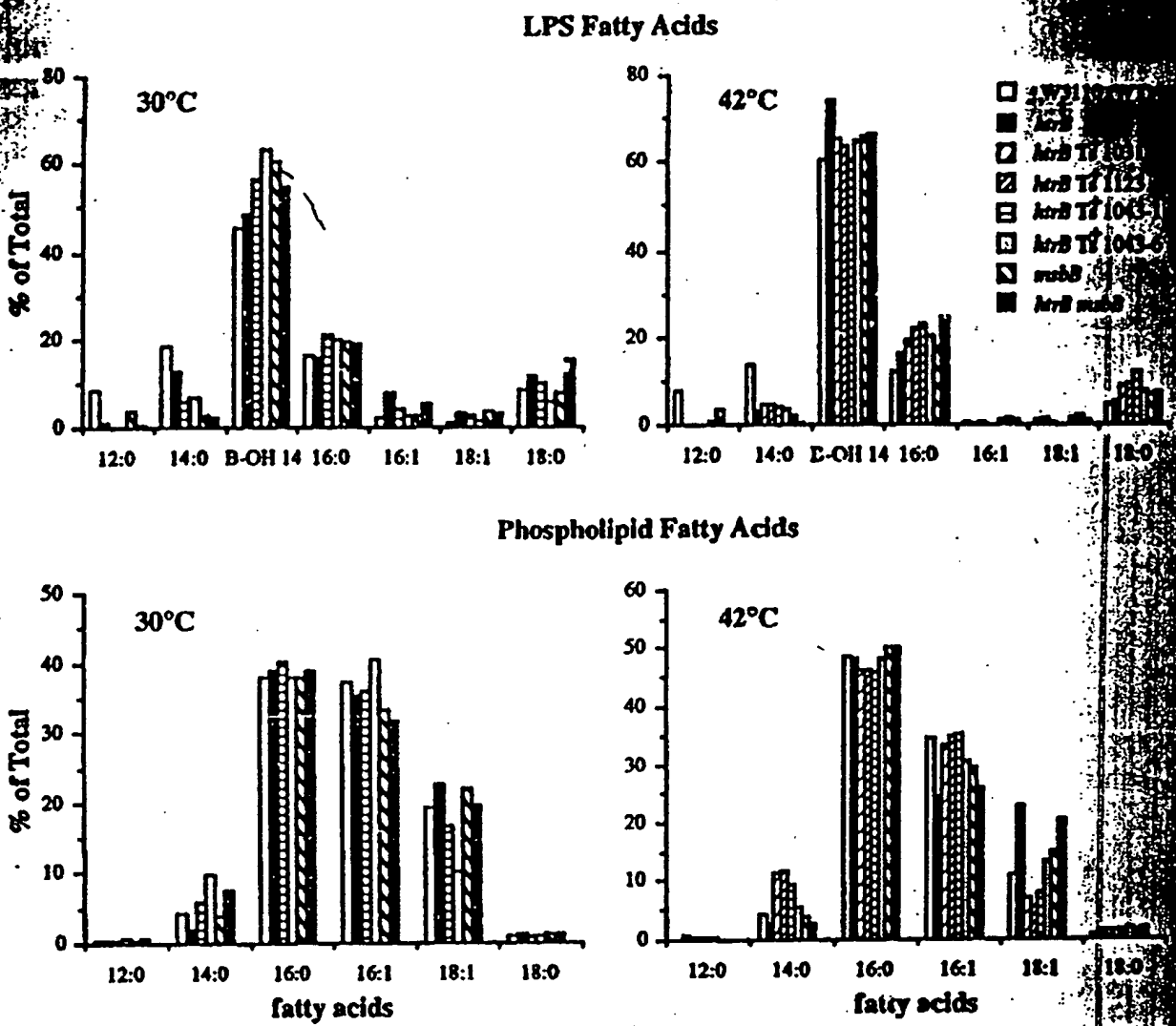


FIG. 4. Fatty acid compositions. Shown are graphical representations of the percent fatty acid composition of phospholipid and LPS fractions from wild-type (WT), *htrB*, *htrB* suppressor strains, *msbB*, and *msbB htrB* bacteria. β-Hydroxymyristic acid is abbreviated as β-OH 14. The phospholipid and LPS fatty acid percentages at 30 and 42°C for wild-type, *htrB*, *msbB*, and *htrB msbB* bacteria are the averages from four independent experiments. The fatty acid percentages for phospholipid and LPS fractions at 42°C for the suppressor strains are the averages from two independent experiments. The fatty acid percentages for phospholipid and LPS fractions at 30°C for the suppressor strains are from a single experiment.

residual enzymatic activity to form β-hydroxymyristic acid, the major fatty acid of LPS.

Because of the observed effects of the *fabE* and *fabD* mutations, we reasoned that the *accBC* suppressor mutations may also alter fatty acid composition and that this might compensate for the effects caused by the lack of HtrB. To determine whether this was the case, we analyzed the fatty acid compositions of both phospholipid- and LPS-enriched fractions isolated from *htrB* bacteria, the suppressor strains, and isogenic wild-type bacteria. It was found that both the LPS and phospholipid fatty acid compositions of *htrB* bacteria were altered (Fig. 4). The LPS fatty acids from *htrB* bacteria grown at either 30 or 42°C exhibited reproducible reductions in lauric acid (12:0) and myristic acid (14:0). At 30°C, there was a slight increase in palmitoleic acid (16:1), and at 42°C, there was an increase in palmitic acid (16:0) and β-hydroxymyristic acid (compare the open and black bars in Fig. 4). Such increases may compensate for the lack of the smaller fatty acids. Rather than reversing these changes, the suppressor mutations actually accentuated the observed decreases in myristic acid (14:0) at 30°C, suggesting that these changes were probably not the cause of *htrB* lethality.

Although the *htrB* mutation had only a slight effect on phospholipid fatty acid composition at 30°C, at 42°C the ratio of the two unsaturated fatty acids, palmitoleic acid (16:1) and *cis*-vaccenic acid (18:1), was considerably altered (compare open and black bars in Fig. 4). The 18:1/16:1 ratio for *htrB* bacteria was 0.93, whereas wild-type bacteria had a ratio of

0.32. However, the total percentage of unsaturated fatty acids remained similar to that for the wild type, 45.8% for wild-type bacteria and 47.3% for *htrB* bacteria. All four suppressors reversed the effect on the 18:1/16:1 ratio, and in the case of the Ts$^+$1031, Ts$^+$1123, and Ts$^+$1043-1 suppressor mutations, there was a slight overcompensation, resulting in 18:1/16:1 ratios between 0.16 and 0.22. Although the ability of the suppressor mutations to reverse the alterations in fatty acid composition indicates that these changes were linked to *htrB* lethality, it is unlikely that these changes were the direct cause of *htrB* lethality, since they are similar to and not as extreme as those changes caused by the Vtr mutation of the *fabF* gene, which has no effect on bacterial viability (9).

In an attempt to further define which of the fatty acid composition changes were associated with *htrB* lethality, we also determined the effects of a null mutation in the *msbB* gene and the effects of an *htrB msbB* double mutation. Because HtrB and MsbB appear to share similar functions but, unlike HtrB, MsbB is not required for growth under any condition tested (25), we reasoned that by comparing changes caused by the *msbB* null mutation with those caused by the *htrB* mutation we could determine which changes were associated with the nonlethal membrane alterations and which were associated with *htrB* lethality.

We found that the *msbB* mutation caused a qualitative alteration in LPS fatty acids similar to that seen with *htrB*. Thus, these changes were most likely associated with nonlethal changes in membrane structure. The *msbB* mutation resulted in a slight change in the phospholipid 18:1/16:1 ratio but not as much as that caused by the *htrB* mutation, a result consistent with the phospholipid fatty acid changes being associated with *htrB* lethality. The *htrB* and *msbB* changes in LPS fatty acids appear to be additive, since the *htrB msbB* double mutation resulted in an effect that was greater than that seen with either single mutation (Fig. 4). At 42°C the double mutation had an effect similar to that of *htrB* alone. This was an expected result, since in all other respects *htrB* has been shown to be epistatic to *msbB* at 42°C (25).

The quantity of phospholipids per milligram of protein. Although the results from the fatty acid analysis suggested that the changes in phospholipid fatty acid composition were associated with *htrB* lethality, no clear relationship between these changes and lethality could be discerned. However, during this analysis we noted an overall increase in the amount of fatty acids present in the phospholipid fraction per milligram of protein from *htrB* bacteria grown at 42°C. To determine whether *htrB* bacteria indeed had increased quantities of phospholipids, we used the hydroxamic quantification method of Stern and Shapiro (38). We standardized the amount of phospholipid to total cellular protein since the quantity of protein per OD_{595} unit of bacteria was not affected by the presence of the *htrB* mutation (data not shown). As shown in Table 2, at 42°C, *htrB* bacteria accumulate more than twice as much phospholipid per milligram of protein as wild-type bacteria do. In each case, the presence of the suppressor mutations inhibited this overproduction, leading to a phospholipid-to-protein ratio that was 94 to 123% of that seen with wild-type bacteria.

The ability of the Ts$^+$1043-1 and Ts$^+$1043-6 mutations to suppress the morphological phenotypes of the *htrB msbB* double mutant at 30°C suggests that this phenotype may also be caused by an increase in phospholipids. However, at 30°C the phospholipid levels for the *htrB msbB* double mutant and both of the single mutants were similar to that of wild-type bacteria (Table 2). Therefore, the morphological changes

TABLE 2. Phospholipid levels for *htrB* and related bacteria at various temperatures

Growth temp (°C)[a]	Strain or relevant genotype	μg of phospholipid/mg of protein	% of wild type
42	W3110 (wild type)	139 ± 10	100
	htrB	326 ± 27	235
	htrB Ts$^+$1031	171 ± 2	123
	htrB Ts$^+$1123	153 ± 8	110
	htrB Ts$^+$1043-1	166 ± 10	119
	htrB Ts$^+$1043-6	130 ± 19	94
	msbB	138 ± 30	99
	htrB msbB	290 ± 30	209
30	W3110 (wild type)	163 ± 14	100
	htrB	146 ± 20	90
	msbB	127 ± 5	78
	htrB msbB	136 ± 9	83

[a] Bacteria were grown at the indicated temperature from an OD_{595} of 0.05 to an OD_{595} of 0.4. For more details, see Materials and Methods.

must be associated with another aspect of membrane biosynthesis that can also be suppressed by the Ts$^+$1043-1 and Ts$^+$1043-6 mutations. Consistent with the *msbB* mutation having no deleterious effects on bacterial growth, no increase in phospholipids at 30 or 42°C was observed (Table 2). Like all other phenotypes tested, *htrB msbB* double-mutant bacteria exhibited the same phenotypes at 42°C as *htrB* mutant bacteria, including the twofold overproduction of phospholipids (Table 2).

Because we have previously proposed that HtrB plays a role in outer membrane function (25), possibly affecting the LPS layer, we also determined the amount of LPS present in *htrB* bacteria. This determination was made by two methods. We first determined the amount of LPS fatty acids per milligram of protein by gas chromatography and found that there was no increase compared with the amount in wild-type bacteria. We also used the thiobarbituric acid method (46) to quantify the amount of 3-deoxy-D-manno-octulosonic acid residues present on LPS and found that there was no increase; wild-type bacteria had 546 ± 47 μg of LPS per mg of protein, and *htrB* bacteria had 591 ± 30 μg of LPS per mg of protein. However, we did find that there was an increase in the amount of LPS in the inner membrane fraction, accompanying a decrease in the amount of LPS in the outer membrane fraction. Whereas 83% of the LPS from wild-type bacteria sedimented with the outer membrane fraction, only 48% of the LPS from *htrB* bacteria sedimented with the outer membrane fraction. Determination of the amount of phospholipid in the two fractions indicated that both the inner and outer membranes contain increased quantities of phospholipids (data not shown). The shift of LPS to the inner membrane fraction was most likely a consequence of increased amounts of phospholipids in the outer membrane, thus decreasing its overall buoyant density, so that it fortuitously sedimented with the inner membrane fraction.

Determination of the rate of phospholipid biosynthesis. To establish the nature of the overproduction of phospholipids in *htrB* bacteria and the means by which the *accBC* mutations suppressed *htrB* lethality, we determined the rate of [1-^{14}C]acetate incorporation into phospholipids. As shown in Fig. 5, the rate of phospholipid biosynthesis was reduced by approximately 30 to 40% in all four suppressor strains compared with that of the wild type. This was an expected result, since all of the suppressor strains exhibited reduced

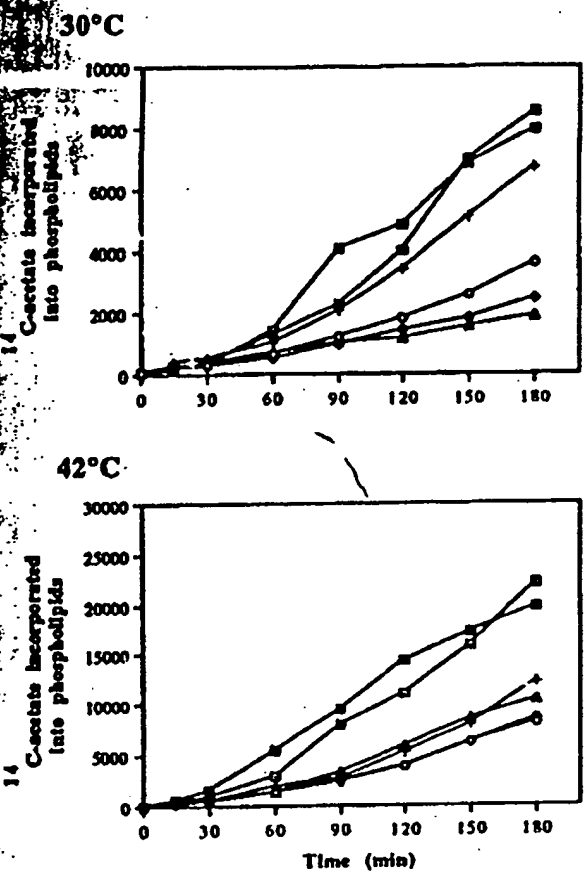


FIG. 5. Rate of phospholipid biosynthesis at 30 and 42°C. Shown is a graph of the [1-^{14}C]acetate incorporated into phospholipids as a function of time for wild-type (□) and *htrB* (■) bacteria and the Ts$^+$1031 (△), Ts$^+$1123 (◇), Ts$^+$1043-1 (○), and Ts$^+$1043-6 (+) suppressor strains.

rates of growth and the Ts$^+$1031 mutation caused a decrease in the transcription of the *accBC* operon.

As mentioned previously, Ts$^+$1031 and Ts$^+$1123 bacteria exhibit a Cs$^-$ phenotype and are unable to form colonies at 30°C. Both the Cs$^-$ and the slow-growth phenotypes are caused by the suppressor mutations and are not affected by the presence of the *htrB* mutation (data not shown). To determine whether the inability of Ts$^+$1031 and Ts$^+$1123 bacteria to form colonies at 30°C was due to a failure to synthesize phospholipids, we also measured the rate of phospholipid biosynthesis at 30°C. As shown in Fig. 5, both of these strains continued to synthesize phospholipids at a rate that was approximately 20 to 30% of that of wild type. Since these strains continued to synthesize phospholipids at 30°C, it is not obvious why Ts$^+$1031 and Ts$^+$1123 bacteria do not form colonies on L-agar plates even after prolonged incubation. The fact that Ts$^+$1043-1 bacteria exhibited a slightly a higher rate of fatty acid biosynthesis at 30°C than the two Cs$^-$ suppressor strains and formed small colonies at 30°C suggests that colony formation may require a threshold amount of phospholipid biosynthesis and that Ts$^+$1031 and Ts$^+$1123 bacteria do not exceed this threshold, but Ts$^+$1043-1 bacteria do.

Because the presence of either the pLac-*accC* or pGB-*accB* plasmid allowed *htrB* bacteria to grow at 42°C, we also measured the rate of phospholipid biosynthesis for wild type and *htrB* strains carrying these plasmids. The presence of either of these plasmids led to a decrease in the rate of fatty acid biosynthesis in both wild-type and *htrB* bacteria. The presence of pLac-*accC* reduced the rate of fatty acid biosynthesis by approximately 65%, whereas pGB-*accB* reduced the rate by approximately 30%. The amount of reduction caused by these two plasmids directly reflected their abilities to allow *htrB* bacteria to grow at 42°C. Mutant *htrB* bacteria carrying pLac-*accC* formed almost wild-type-size colonies at 42°C, whereas those carrying pGB-*accB* formed only small colonies. The reduction in fatty acid biosynthesis caused by pGB-*accB* may be enough to permit colony formation of *htrB* bacteria at 42°C but not enough for rapid growth. As proposed above, the presence of either of these plasmids probably disrupts the stoichiometric balance of the subunits composing the acetyl-CoA carboxylase complex. This disruption and consequent reduction in fatty acid biosynthesis may also explain why the *accB* gene cannot be cloned alone on higher-copy-number plasmids. The increased amounts of BCCP may disrupt the complex to such a degree that fatty acid biosynthesis is dramatically affected.

At both 30 and 42°C, *htrB* bacteria exhibited wild-type rates of phospholipid biosynthesis. This indicates that the overproduction of phospholipids may not be the result of an increased rate of phospholipid biosynthesis, but rather it may reflect the uncoupling of the rate of phospholipid biosynthesis from the rate of growth. Consistent with this, when *htrB* bacteria were shifted to 42°C, they continued to grow at a rate similar to that at 30°C, as judged by OD_{595} (9) (Fig. 2). However, *htrB* bacteria synthesized phospholipids at the rate required for wild-type bacteria to grow at 42°C. Unlike the rate of phospholipid biosynthesis, the rate of protein synthesis remained coupled to the rate of growth at high temperatures (data not shown). Thus, the increase in phospholipid levels per milligram of protein was actually the consequence of protein biosynthesis remaining coupled to the reduced rate of growth and phospholipid biosynthetic rates increasing with temperature, independently of growth rate.

The uncoupling between growth and phospholipid biosynthesis rates is best exemplified by the ratio of incorporated [1-^{14}C]acetate counts into phospholipid per milligram of protein. For wild-type bacteria this ratio was 2,500 cpm/mg of protein. In contrast, the ratio for *htrB* bacteria was 16,400 cpm/mg of protein. The *accBC* suppressor mutations appear to reduce phospholipid biosynthesis so that growth and phospholipid biosynthesis are once again coupled. The corresponding ratios for Ts$^+$1031 and Ts$^+$1041-6 bacteria were 3,600 and 3,100 cpm/mg of protein, respectively, much reduced compared with that for *htrB* bacteria and similar to those for the wild type.

DISCUSSION

Four single-copy extragenic suppressors of *htrB* have been isolated and mapped to the *accBC* operon, which codes for BCCP and biotin carboxylase. These two proteins associate with a heterodimer of carboxyltransferase to form the acetyl-CoA carboxylase enzyme complex. This complex catalyzes the first step in fatty acid biosynthesis, namely, the carboxylation of acetyl-CoA to form malonyl-CoA. Two of the four suppressor mutations, Ts$^+$1123 and Ts$^+$1043-6,

were mapped to the *accC* gene, encoding biotin carboxylase, whereas the Ts⁺1043-1 allele was mapped to the *accB* gene, encoding BCCP. The fourth mutation, Ts⁺1031, was identified as an insertion of an IS*1* transposable element in the promoter region of the operon.

The effect of this IS*1* element was a large reduction of *accBC* operon transcription. We were surprised to find that such a large change in mRNA levels had only a small effect on the biotinylated BCCP levels at 42°C. One possible explanation for this is that the *accB* gene is under translational regulation and, hence, a low intracellular level of mRNA may have little effect on BCCP levels. The unusually long, 5′-untranslated region of this mRNA (29) could serve such a function. Alternatively, if a constant level of biotinylated BCCP is maintained in the cell (irrespective of the quantity of unbiotinylated BCCP), changes in mRNA levels may have little effect on the levels of biotinylated BCCP. One argument against this latter suggestion is that Fall and Vagelos (10) showed that most of the BCCP isolated from *E. coli* is in the biotinylated form. However, if unbiotinylated BCCP is unstable, either in vivo or during the isolation procedure, it would appear that a majority of the BCCP in the cell is biotinylated.

Whether the effects of the Ts⁺1031 mutation were mediated through a small decrease in both BCCP and biotin carboxylase levels or through a larger decrease in biotin carboxylase levels alone is not known at this time. At 30°C, the Ts⁺1031 mutation must affect the levels of both biotin carboxylase and BCCP, since neither pGB-*accB* nor pLac-*accC* complemented the Cs⁻ phenotype of Ts⁺1031; only the presence of the pKS-1031 plasmid, which carries both genes, resulted in growth at 30°C. It appears that suppression can be mediated through either of these gene products, since the Ts⁺1123 and Ts⁺1043-6 alleles were identified as mutations in the *accC* gene and Ts⁺1043-1 was identified as a mutation in *accB*. These results also suggest that suppression was mediated through the activity of acetyl-CoA carboxylase enzyme complex as a whole, rather than through any one of its individual components.

Because these suppressor mutations mapped to an operon whose products are involved in phospholipid biosynthesis, we studied the effects of the *htrB* null mutation on this process. When *htrB* bacteria are grown at temperatures above 33°C in rich media, they lose viability rapidly (23). This loss of viability is associated with a twofold increase in the amount of phospholipid per milligram of protein. The overproduction of phospholipids was the consequence of synthesizing phospholipids at a rate that appears to be in excess of that required to accommodate the reduced growth rate of *htrB* bacteria at 42°C. This uncoupling of phospholipid biosynthesis and growth rates appears to be integral part of *htrB* lethality at high temperatures, since the suppressor mutations most likely rescue by reducing the rate of phospholipid biosynthesis, thus matching the reduced rate of growth. The ability of either the pGB-*accB* or pLac-*accC* plasmid alone to rescue the lethal phenotype of *htrB* bacteria also appears to be the result of a decrease in the rate of phospholipid biosynthesis, presumably caused by an imbalance in the levels of the individual subunits of the complex.

The *htrB* mutation also affected the fatty acid composition of both LPS and phospholipids. At both 30 and 42°C, the LPS fatty acids from *htrB* bacteria were relatively depleted in lauric and myristic acid residues but relatively enriched in the larger fatty acid residues compared with those from the wild-type bacteria. The absence of MsbB, a protein with a sequence similar to that of HtrB, had a similar effect on LPS fatty acids. These changes in LPS fatty acid composition cause or reflect other changes in the LPS [illegible] result in the increased deoxycholate resistance exhibited by *htrB* and *msbB* bacteria (25). Consistent with this, the suppressor mutations did not reverse the deoxycholate resistance, nor did they reverse the changes to LPS fatty acid composition. The deoxycholate resistance and alterations in LPS fatty acid composition are the only phenotypes of *htrB* that we have been able to identify at permissive temperatures. These results suggest that LPS synthesis may be the primary target of the *htrB* mutation. Unlike the changes in phospholipid composition, the changes to LPS fatty acid composition were not accompanied by changes in the quantity of LPS. This could indicate that whereas phospholipid biosynthesis is limited by the rate of fatty acid biosynthesis, LPS biosynthesis is controlled at some other step in its biosynthesis.

In contrast to the changes to LPS, the phospholipid fatty acid composition changes exhibited by *htrB* bacteria at 42°C were reversed by the presence of the suppressor mutations. As mentioned previously, we do not believe that these changes cause *htrB* lethality, because the observed changes in fatty acid composition are reminiscent of those exhibited by bacteria with the Vtr mutation in the *fabF* gene, encoding β-ketoacyl-acyl carrier protein synthase II, which are able to grow at all temperatures (9). This enzyme elongates palmitoleic acid, forming *cis*-vaccenic acid. The activity of the wild-type enzyme itself is altered by temperature, such that as the temperature rises the activity of the enzyme decreases, leading to a relative decrease in *cis*-vaccenic acid levels at higher temperatures (13). The Vtr mutation results in an increase in the activity of this enzyme at all temperatures such that high levels of *cis*-vaccenic acid are synthesized independently of growth temperature (9). Similar to the Vtr mutation, the imbalance in phospholipid biosynthesis and growth rates caused by the lack of HtrB may actually increase the activity of β-ketoacyl-acyl carrier protein synthase II such that *cis*-vaccenic acid levels are increased at the expense of palmitoleic acid levels. The decrease in smaller fatty acids in the LPS fractions from the suppressor strains could be the result of the decrease in fatty acid biosynthesis altering the balance between the utilization of the smaller fatty acids for elongation and their incorporation into the lipid A portion of LPS.

Originally, we interpreted the formation of the bulges and filaments by *htrB* bacteria at the nonpermissive temperatures to be the consequence of changes in cell wall structure (23). Although the *htrB* mutant may have an altered cell wall structure, because of our finding of an excess of phospholipids in *htrB* bacteria we now suggest that the formation of the bulges may be more analogous to the formation of bulges caused by an overproduction of poly-β-hydroxybutyrate (37). Poly-β-hydroxybutyrate is a homopolymer of D-(−)-3-hydroxybutyrate produced as a storage molecule by a wide variety of bacteria. *E. coli* does not normally produce this polymer. However, when the genes encoding the biosynthetic enzymes for the polymer are expressed in *E. coli*, large quantities of it are produced, constituting up to 80% of its dry weight (37). Such high levels of poly-β-hydroxybutyrate can lead to altered morphologies, including the formation of bulges and filaments (37). *E. coli* may respond to the presence of excess phospholipids in *htrB* bacteria in the same manner in which it deals with the large quantities of this polymer, in both cases leading to the formation of bulges and filaments.

Taking all of our data together, it appears that the [illegible]

Ts⁻ phenotype of *htrB* is caused by the combination of an overall reduced growth rate and its uncoupling from the rate of phospholipid biosynthesis at high temperatures. Because *htrB* bacteria can grow at high temperatures under slow-growth conditions (23), such as in minimal media, we believe that the Ts⁻ phenotype exhibited by these bacteria is not wholly caused by the growth temperature but instead is a consequence of the increased growth rate at higher temperatures. When *htrB* bacteria are grown in rich media at temperatures above 33°C, they continue to grow at a rate that is similar to the rate at which they were growing at the permissive temperature of 30°C. The inability to adjust their growth rate in rich media at high temperatures suggests that in the absence of HtrB, the rate of some essential process is limited.

It is not clear why phospholipid biosynthesis does not remain coupled to the rate of growth in *htrB* bacteria. Growth rate limitation in itself does not lead to uncoupling, since a variety of mutant strains exhibit slow-growth phenotypes without associated lethality (4, 7, 36, 44, 47). It appears that HtrB is uniquely involved in the coupling of phospholipid biosynthesis and growth rate under conditions of rapid growth. If the *htrB* mutation primarily affects the LPS layer of the outer membrane, as we have previously proposed (25), the intriguing possibility exists that HtrB provides a link between the regulation of phospholipid biosynthesis, LPS biosynthesis, and bacterial growth.

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EPARATIONS

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[25] Bacterial Lipopolysaccharides

Extraction with Phenol–Water and Further Applications of the Procedure

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Introduction

Liquid phenol is known to be an excellent solvent for many proteins. The partition coefficient in biphasic phenol–water mixtures very often allows an almost complete extraction of proteins from aqueous solutions under controlled conditions of pH and ionic strength in a one-step operation. In contrast, polysaccharides, mucopolysaccharides, lipopolysaccharides, and nucleic acids are usually water-soluble but phenol-insoluble. Various polysaccharides can be precipitated from aqueous solution by adding liquid phenol (see, for example, *1*). Phenol is a weak acid, the dissociation constant at 18–19° in water being $1.1\text{–}1.2 \times 10^{-10}$ (*2*). Mixtures of phenol and water have a high dielectric constant. These facts form the basis of a method of partition of proteins and polysaccharides and/or nucleic acids between phenol and water. Separation of proteins from polysaccharides and nucleic acids by phenol–water is often effected by both the favorable partition coefficient and the dissociation power of phenol–water mixtures.

Morgan and Partridge (*3*) showed that diethylene glycol extracts (endotoxic or whole O-antigenic complex) of various Enterobacteriaceae, such as *Shigella dysenteriae* and *Salmonella typhosa*, are composed of specific polysaccharide, protein, and lipid material (see Vol. V [24]). In 90% liquid phenol solution, the whole complex dissociated. If the reaction mixture was dialyzed against water, the protein precipitated while the undegraded polysaccharide remained in the final water solution. The same method was applied by Goebel and co-workers (*4*) for the

dissociation of the protein–polysaccharide complex from *Shigella sonnei* into phenol-soluble protein and water-soluble lipopolysaccharide. Goebel and Barry (*5*) also used this method for the dissociation of the colicine K-containing complex of *E. coli* K_{235} into protein and lipopolysaccharide.

Palmer and Gerlough (*6*), in attempts to develop suitable direct extraction procedures for enterobacterial somatic polysaccharide antigens, treated whole bacteria with liquid phenol followed by water extraction. Phenol caused the dissociation of the O-antigenic complex in the bacterial cell wall in such a manner that subsequent treatment with water led to the extraction of highly antigenic undegraded polysaccharide of low protein content. For complete polysaccharide extraction, the two-step procedure had to be repeated several times. The Palmer–Gerlough method was also successfully applied in the field of Gram-positive bacteria by M. Heidelberger and co-workers (*7*) for the extraction of capsular polysaccharides from pneumococci; these were then used as powerful antigens in man (*8*).

Westphal and co-workers (*9*) later showed that the Palmer–Gerlough extraction (*6*) can be simplified by shaking bacteria directly in an *emulsion of equal volumes of liquid phenol and water* for a few minutes at low temperature (5–10°). If the mixture is centrifuged, it separates into an upper water layer, a lower phenol layer, and an insoluble residue, the water phase containing the totality of the undegraded polysaccharide (lipopolysaccharide) and nucleic acid (procedure A in ref. *9*). The same procedure was applied by Burton and Carter (*10*) for the extraction of *E. coli O 111* cells; these workers further hydrolyzed the purified protein-free lipopolysaccharide into lipid [lipid A (*11*, *12*)] and degraded polysaccharide. Tauber and Garson (*13*) also made use of the method for the extraction of the endotoxic lipopolysaccharide from *Neisseria gonorrhoeae*. The authors vigorously stirred the mixture in a Waring Blendor for 8 min. During this period, most of the cells disintegrated, and the whole antigenic complex dissociated. The temperature of the mixture rose from about 10° at the beginning to about 40° at the end of stirring. After centrifugation at room temperature, the water and phenol layers were separated. The water phase contained practically all the lipopolysaccharide.

Lipopolysaccharides extracted from bacteria with cold emulsions of phenol–water, however, often still contain varying amounts of firmly bound protein.

At temperatures above 68°, phenol and water are miscible at any proportion (*14*). On cooling, the homogeneous mixture separates into two layers, the upper water phase (saturated with phenol) and the

Procedure

Procedure I (*9, 11, 15, 34*)

Gram-negative bacteria, after cultivation in suitable media, are centrifuged, and the sediment is washed with saline. The bacteria are killed by adding acetone and/or lyophilized from the frozen state.

Phenol–water Extraction

Twenty g. (dry weight) of bacteria, for example, Enterobacteriaceae (*Escherichia, Salmonella,* and so on), are suspended in 350 ml. of water at 65–68° (on a water bath); 350 ml. of 90% phenol, preheated to 65–68°, is then added with vigorous stirring, and the mixture is kept 10–15 min. at 65°. After cooling to about 10° by placing the vessel in an ice bath, the emulsion is centrifuged at 3000 rpm. for 30–45 min., which results in the formation of three layers: a water layer, a phenol layer, and an insoluble residue, the latter sometimes forming a layer at the phenol–water interphase. The water phase is sucked off, and the phenol layer and the insoluble residue are treated at 65–68° with another 350 ml. of water as described above. The combined water extracts are dialyzed 3–4 days against distilled water to remove phenol and small amounts of low-molecular-weight bacterial substances. The dialyzed, slightly opalescent solution, which contains the lipopolysaccharide and ribonucleic acid, is concentrated at 35–40° under reduced pressure to a volume of about 100 ml. After centrifugation for the removal of traces of insoluble material, the water solution is freeze-dried to give an almost white fluffy powder; yield 1.6–2.0 g. (8–10% of the dry weight of the bacteria). The crude extract is composed of about 40–50% of lipopolysaccharide (endotoxic O-antigen) and 50–60% of bacterial ribonucleic acid (RNA).

Removal of Nucleic Acid

The lyophilized crude extract is dissolved in water to give a 3% solution which is centrifuged for 6–8 hr. at 80,000 × g. The sediment is suspended in water, and the suspension is recentrifuged 2–3 times at 105,000 × g. for 3 hr. each. The final sediment is taken up in a minimum amount of water and freeze-dried; yield of bacterial lipopolysaccharide, 300–500 mg. (1.5–2.5% of the dry weight of the bacteria), containing 3% of nucleic acid.

It is known that polyanionic substances form water-insoluble salts with cationic detergents, such as cetyltrimethylammonium bromide ("cetavlon"). However, these salts dissolve in inorganic salt solutions, for example, sodium chloride, the solubility being dependent upon the

ionic strength (and pH) of the medium. For a review see ref. *35*. Using the "cetavlon" technique, Jones (*36*) purified bacterial nucleic acids, and Scott (*37*) fractionated crude heparin preparations and other acidic polysaccharides (Vol. V [11]). On the basis of these results, it was found (*17*) that mixtures of bacterial lipopolysaccharides and nucleic acids, as obtained after phenol–water extraction (Procedure I), can be separated according to the stronger acidic character of nucleic acids in comparison to lipopolysaccharides, which are weakly anionic in character because of their low content of phosphoric acid ester groups (see *11*, *12*, *28*).

This technique can be applied in various ways. (a) The lipopolysaccharide sediment after one or two ultracentrifugations often still contains a few per cent of nucleic acid. By "cetavlon" precipitation, the small amount of RNA can be separated to give an RNA-free lipopolysaccharide (with no absorption maximum at 260 mμ) (Procedure II). (b) The nucleic acid fraction of the supernatant of the ultracentrifuged lipopolysaccharide sediment always contains appreciable amounts of bacterial lipopolysaccharide which, in combination with nucleic acid, does not sediment at 30,000–40,000 rpm. (see above). By "cetavlon" precipitation of the nucleic acid, the remaining lipopolysaccharide can be obtained in purified form. It was found (*17*) that this lipopolysaccharide fraction sometimes differs quantitatively in composition as compared to the first sedimented lipopolysaccharide. For example, the lipopolysaccharide of *E. coli O 111:B4*, prepared according to Procedure I, was found to have a content of 14% of 3,6-dideoxy-L-*xylo*-hexose (colitose, 3-deoxy-L-fucose), while the remaining lipopolysaccharide from the nucleic acid fraction in the supernatant, after "cetavlon" fractionation, had a colitose content of 27–28%. Whether this is an indication for more than one specific lipopolysaccharide in *E. coli O 111:B4* organisms remains to be clarified (see also *37a*). (c) The crude lipopolysaccharide–nucleic acid extract (according to Procedure I) is directly fractionated with "cetavlon" to give the bulk of RNA-free lipopolysaccharide (Procedure III).

Procedure II

One g. of crude lipopolysaccharide, containing 2–5% of RNA, is dissolved in about 150 ml. of water; 15 ml. of a 2% aqueous "cetavlon" solution is added, and the mixture is stirred for about 15 min. at room temperature. The turbid mixture is then centrifuged for 20 min. at 3000 rpm. to remove the precipitated RNA. The opalescent supernatant is lyophilized, and the fluffy residue is dissolved in 50–60 ml. of 0.5 *M* sodium chloride. The solution is poured into a tenfold volume of ethanol

to precipitate the lipopolysaccharide, excess "cetavlon" remaining in solution. After standing 1–2 hr. at 0–4°, the precipitate is centrifuged and redissolved in water. After dialysis for 2 days against deionized water to remove sodium chloride, the solution is freeze-dried (Vol. V [17]); yield about 900 mg. of RNA-free lipopolysaccharide.

Procedure III

The lyophilized crude lipopolysaccharide–nucleic acid extract from the water phase of the phenol–water extraction (Procedure I) is dissolved in 0.5 *M* sodium chloride to give a 0.5–1% solution. A 2% solution of "cetavlon" in 0.5 *M* sodium chloride is added with stirring until the proportion of "cetavlon" to crude extract is about 1.5:1. The solution is now gradually diluted with water, and precipitates are collected by centrifugation as they appear. The RNA–"cetavlon" salt precipitates at a sodium chloride concentration of about 0.3 *M*. The final dilute solution is lyophilized (Vol. V [17]) and taken as the last fraction. The fractions are dissolved in 0.5 *M* sodium chloride and poured into a tenfold volume of ethanol. After centrifugation, the sediment is dissolved in water, dialyzed, and freeze-dried (Vol. V [17]); yield of RNA-free lipopolysaccharide 30–40% of the crude extract.

Fractional "cetavlon" precipitation according to Procedure III proved to be of special value in cases, for example, in the *Salmonella* and *Escherichia* species, in which the water phase after phenol–water extraction, sometimes contained an additional acid mucopolysaccharide in addition to lipopolysaccharide and nucleic acid (*17a*).

Another means of obtaining nucleic acid-free bacterial lipopolysaccharide arose from the finding (*38*) that the phenol–water extraction of formalin-killed *Salmonella* bacteria gives a water phase containing lipopolysaccharide and only small amounts or no RNA. A further investigation (*39*) showed that bacterial RNA, after treatment of the bacteria with diluted formaldehyde (0.1–0.5%), is no longer extractable by phenol–water (Procedure I), probably because cross-linkages are formed between RNA and bacterial protein, giving rise to phenol–water-insoluble complexes. The formalin variation of the phenol–water extraction, however, needs to be investigated in more detail.

Further Applications of the Phenol–water Procedure

Partition of protein and polysaccharide or lipopolysaccharide between phenol and water can be applied for the dissociation and separation of specific precipitates of polysaccharide antigens with antibody (*40*). In principle, the precipitate is dispersed in water, and an equal volume of liquid phenol is added with stirring. After separation of the two phases

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by centrifugation, the water layer contains the antibody-free polysaccharide antigen, which can be isolated and analyzed. The method allows the purification of polysaccharide antigens by aid of specifically precipitating antibodies (*32, 40*); it thus allows the fractionation of polysaccharide antigens according to their serological specificity. Homan and Lens (*41*) purified crude, protein-containing extracts of heparin by partition between phenol and water. From the water phase, which proved to be free of protein, purified heparin could be isolated.

Recently, Broberger and Perlman (*42*) were able to obtain an autoantigen from colonic and other tissues of new-born babies, involved in the pathogenesis of fatal ulcerative colitis. The antigen was extracted with phenol–water at 65° and appeared to be mainly polysaccharide in nature.

On the basis of our findings (*9*), Schramm and co-workers (*43*) developed a method for the dissociation of tabacco mosaic virus (TMV) nucleoprotein into phenol-soluble protein and water-soluble undegraded ribonucleic acid. They were then able to show for the first time that the protein-free TMV ribonucleic acid is the infective unit of the virus. These results prompted a wide application of the phenol–water method to many viruses, and it was clearly shown that the respective nucleic acids acted as the carriers of viral activity. For a review see ref. *44*.

Kirby (*45, 46*) showed that protein-free RNA and DNA (deoxyribonucleic acid) can be extracted from tissues of higher organisms by aid of a modified phenol–water procedure. Normally only RNA is extracted, as with bacteria. If lipophilic and complex-forming salts, such as *p*-aminosalicylate, are added, protein-free DNA can also be extracted. The mixture of RNA and DNA can later be separated by specific precipitation of the DNA fraction.

Nucleic acids (RNA and DNA) of many viruses were extracted from infected tissues, either with cold emulsions or with heated mixtures of phenol and water, and shown to be the infective agents of the virus (as examples, see refs. *47–54*).

From phenol–water dissociated TMV nucleoprotein Anderer (*55*) was able to recover the TMV protein from the phenol solution. The isolated protein recombined with TMV nucleic acid to give crystalline TMV nucleoprotein. This indicates that the protein did not irreversibly denature in liquid phenol. Kickhöfen (*56*) recently demonstrated that various enzymes, ribonuclease, chymotrypsin, trypsin, lysozyme and others, after dissolving in liquid phenol, can also be quantitatively reextracted by a similar technique without loss of enzymic activity. Some enzymes even withstand heating of their phenol solutions up to 80–100°.

The phenol–water extraction, therefore, may probably be not only

applicable for the isolation and purification of polysaccharides, lipopolysaccharides, or nucleic acids, but, in certain instances, also for proteins.

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APPENDIX IV

Cited Statute and Case Law

I. Statute

The first paragraph of 35 U.S.C. § 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

II. Case Law

Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 42 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1997).

Decisions of the United States Courts and of the United States Patent and Trademark Office in Patent, Trademark, and Copyright Cases

U.S. Court of Appeals
Federal Circuit

Genentech Inc. v. Novo Nordisk A/S

No. 96-1440

Decided March 13, 1997

PATENTS

1. Patentability/Validity — Specification — Enablement (§115.1105)

Specification of patent in suit would not have enabled person of ordinary skill in art at time of filing to use cleavable fusion expression to make human growth hormone without undue experimentation, since specification merely describes three or four applications for which cleavable fusion expression is generally well-suited, and names enzyme that might be used as cleavage agent as well as sites at which it cleaves, and thus does not describe specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work, and since evidence does not support patentee's contention that disclosure of DNA encoding hGH, combined with prior art cleavable fusion expression techniques applied to non-human proteins, would enable practice of claimed method.

2. Patentability/Validity — Specification — Enablement (§115.1105)

Rule that specification need not disclose what is well known in art means only that omission of minor details does not cause specification to fail to meet enablement requirement, and is not substitute for basic enabling disclosure; if there is no disclosure of any starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art.

3. Patentability/Validity — Specification — Enablement (§115.1105)

Specification that states problem of obtaining human growth hormone from precursor containing added protein material does not enable claim for method of producing hGH using cleavable fusion expression, since specification discloses method in which problem is solved by obtaining hGH unaccompanied by leader sequence or other extraneous proteins, but does not provide specific enabling disclosure for obtaining hGH by cleaving hGH-containing protein as recited in claim.

4. Patentability/Validity — Specification — Enablement (§115.1105)

Fact that no one had been able to produce any human protein via cleavable fusion expression as of application date of patent in suit undermines patentee's contention that specification's disclosure of DNA sequence encoding human growth hormone and single example enzyme and its cleavage site, without more, would have enabled one skilled in art to have used claimed cleavable fusion expression method to make hGH without undue experimentation; moreover, if disclosure of useful conjugate protein and method for its cleavage were clearly within skill of art, as patentee asserts, it would have been expressly disclosed in specification, and in customary detail.

Particular patents — Chemical — Human growth hormone

5,424,199, Goeddel and Heyneker, human growth hormone, invalid for lack of enablement.

Appeal from the U.S. District Court for the Southern District of New York, Motley, J.

Action by Genentech Inc. against Novo Nordisk A/S, Novo Nordisk of North America Inc., and Novo Nordisk Pharmaceuticals Inc. for patent infringement. From grant of plaintiff's motion for preliminary injunction, defendants appeal. Injunction vacated; patent held invalid as matter of law for failure of specification to enable practice of claimed method.

Prior decision: 37 USPQ2d 1773.

Leora Ben-Ami, John E. Kidd, Nicholas L. Coch, Joseph Ferraro, Philip E. Roux, and Gerard P. Norton, of Rogers & Wells, New York, N.Y.; Ryan Trainer, of Rogers & Wells, Washington, D.C., for plaintiff-appellee.

Albert L. Jacobs Jr., Jesse D. Reingold, Gerard F. Diebner, Daniel A. Ladow, Brad S. Needleman, and Andrew T. Solomon, of Graham & James, New York; John C. Vassil, Kurt E. Richter, and Kenneth H. Sonnenfeld, of Morgan & Finnegan, New York, for defendants-appellants.

Before Archer chief judge, and Lourie and Bryson, circuit judges.

Lourie, J.

Novo Nordisk A/S, Novo Nordisk of North America, Inc., and Novo Nordisk Pharmaceuticals, Inc. (collectively "Novo") appeal from the order of the United States District Court for the Southern District of New York, issuing a preliminary injunction in favor of Genentech, Inc., enjoining Novo from importing, marketing, using, selling, offering for sale or distributing its Norditropin®-brand recombinant human growth hormone (hGH) product. *Genentech, Inc. v. Novo Nordisk A/S*, 935 F. Supp. 260 (S.D.N.Y. 1996). Because the district court's conclusion that Genentech had demonstrated a likelihood of success on the merits was based on an error of law and because its remaining findings were premised on this error, we vacate the injunction.

BACKGROUND

This consolidated patent infringement action was first brought in the United States District Court for the Southern District of New York on November 30, 1994. On May 12, 1995, Genentech moved for a preliminary injunction under U.S. Patent 4,601,980 to prevent Novo from importing, marketing, using, selling, offering for sale or distributing in the United States its Norditropin®-brand recombinant hGH product. The district court granted Genentech's motion and issued an injunction. *Novo Nordisk of North Am., Inc. v. Genentech, Inc.*, No. 94 Civ. 8634 (CBM), 1995 U.S. Dist. LEXIS 12588, 1995 WL 512171 (S.D.N.Y. Aug. 28, 1995).

On appeal this court vacated the injunction. *Novo Nordisk of North Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 37 USPQ2d 1773 (Fed. Cir. 1996). We held that the district court clearly erred in finding that Genentech established a likelihood of proving infringement of the '980 patent because that finding was based on an improper construction of claim 2 of the patent. Based upon the specification and prosecution history, we concluded that because the claim used the phrase "human growth hormone unaccompanied by . . . other extraneous protein," it was limited to processes for directly expressing either hGH or met-hGH. *Id.* at 1371, 37 USPQ2d at 1779. Because the parties agreed that Novo did not use direct expression to produce these proteins, we concluded that Novo did not infringe the patent. *Id.*

Upon returning to the district court, Genentech asserted its newly issued U.S. Patent 5,424,199. The '199 patent has the same specification as the '980 patent and contains a single claim directed to:

> [a] method of producing a protein consisting essentially of amino acids 1-191 of human growth hormone comprising:
>
> (a) expressing in a transformant bacterium, DNA coding for a human growth hormone conjugate protein, which conjugate protein consists essentially of amino acids 1-191 of human growth hormone as set forth in combined Figs. 1 and 3 unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto and an additional amino acid sequence which is specifically cleavable by enzymatic action, and
>
> (b) cleaving extracellularly said conjugate protein by enzymatic action to produce said protein consisting essentially of amino acids 1-191 of human growth hormone.

This claim differs from the claim adjudicated in the prior case in reciting that the encoded protein has an additional amino acid sequence and includes the step of cleaving this conjugate protein. This process of expressing a DNA encoding a conjugate protein and using an enzyme to cleave off an undesired portion of that protein is generally known as cleavable fusion expression. The parties agree that Novo uses cleavable fusion expression to produce hGH. *Id.*

On June 27, 1996, after conducting a twelve-day evidentiary hearing, the district court again issued a preliminary injunction, this time based upon the '199 patent, enjoining Novo from importing, marketing, using, selling, offering for sale, or distributing in the United States its Norditropin®-brand recombinant hGH product. *Genentech v. Novo Nordisk A/S*, 935 F. Supp. 260 (S.D.N.Y. 1996). The district court based its decision upon, *inter alia*, a finding that Genentech would likely overcome Novo's defense that the '199 patent was invalid for lack of an enabling disclosure under 35 U.S.C. § 112, ¶ 1 (1994).

Novo appeals to this court, challenging the grant of the preliminary injunction.[1] We have jurisdiction pursuant to 28 U.S.C. § 1292 (c) (1994).

DISCUSSION

The grant or denial of a preliminary injunction pursuant to 35 U.S.C. § 283 is within the discretion of a district court. *We Care, Inc. v. Ultra-Mark Int'l Corp.*, 930 F.2d 1567, 1570, 18 USPQ2d 1562, 1564 (Fed. Cir. 1991). Accordingly, a trial court's decision granting a preliminary injunction will be overturned on appeal only upon a showing that the court abused its discretion. *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 772, 28 USPQ2d 1378, 1380 (Fed. Cir. 1993). Such an abuse of discretion may be established by showing that the court made a clear error of judgment in weighing relevant factors or exercised its discretion based upon an error of law or clearly erroneous factual findings. *Id.*

As the moving party, Genentech had to establish its right to a preliminary injunction in light of four factors: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships; and (4) the impact of the injunction on the public interest. *Nutrition 21 v. United States*, 930 F.2d 867, 869, 18 USPQ2d 1347, 1348-49 (Fed. Cir. 1991); *Hybritech Inc. v. Abbott Lab.*, 849 F.2d 1446, 1451, 7 USPQ2d 1191, 1195 (Fed. Cir. 1988).

A. *Likelihood of Success on the Merits*

In order to demonstrate that it has a likelihood of success, Genentech must show that, in light of the presumptions and burdens that will inhere at trial on the merits, (1) it will likely prove that Novo infringes the '199 patent and (2) its infringement claim will likely withstand Novo's challenges to the validity and enforceability of the '199 patent. *See New England Braiding Co. v. A.W. Chesterton Co.*, 970 F.2d 878, 882-83, 23 USPQ2d 1622, 1625-26 (Fed. Cir. 1992).[2] In other words, if Novo raises a "substantial question" concerning validity, enforceability, or infringement (*i.e.*, asserts a defense that Genentech cannot show "lacks substantial merit") the preliminary injunction should not issue. *Id.* More specifically, with regard to Novo's validity defenses, the question on appeal is whether there is substantial merit to Novo's assertion that the '199 patent claim fails to meet the requirements of 35 U.S.C. § 112, ¶ 1 (1994).

Novo argues that the district court's findings regarding validity under § 112, ¶ 1, are clearly erroneous because it presented clear and convincing evidence that the patent specification would not have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation. Novo also argues that the specification fails to contain a written description of the claimed invention. Regarding enablement, Novo argues that the patent is invalid because it does not contain sufficient detail concerning the practice of the claimed method. Novo argues that the mere generic statement of the possibility of cleavable fusion

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[1] On July 3, Novo moved for an emergency stay of the injunction pending disposition of this appeal. On August 1, we denied Novo's motion and reinstated the injunction. However, after having heard oral argument in this case, we reconsidered the motion and reinstated the stay of the injunction.

[2] A patent is presumed valid, 35 U.S.C. § 282 (1994), and a party challenging validity must prove invalidity by clear and convincing evidence. "However, the presumption does not relieve a patentee who moves for preliminary injunction from carrying the normal burden of demonstrating that it will likely succeed on all disputed liability issues at trial, even when the issue concerns the patent's validity." *New England Braiding*, 970 F.2d at 882, 23 USPQ2d at 1625 (citing *Nutrition 21*, 930 F.2d at 869, 18 USPQ2d at 1349).

expression, along with the DNA sequence encoding hGH, a single enzyme (trypsin) for cleaving undisclosed conjugate proteins, and a statement of that enzyme's cleavage sites as being potential amino acid extensions conjugated to hGH is not an enabling disclosure commensurate in scope with the claim. Genentech responds that all of the district court's factual findings regarding enablement are supported by the record. More specifically, Genentech argues that those skilled in the art of recombinant protein expression and purification at the time of filing, July 5, 1979, would have been able to use cleavable fusion expression to produce hGH without undue experimentation by using the teachings of the specification along with methods and tools well known in the art. We conclude that Novo has raised more than a substantial question concerning the validity of the '199 patent. In fact, it has shown that the patent is invalid.

Section § 112, ¶ 1, provides, in relevant part that:

> [t]he specification shall contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . .

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988).

[1] The question before us is whether the specification would have enabled a person having ordinary skill in the art at the time of filing to use cleavable fusion expression to make hGH without undue experimentation. There is no dispute that the portion of the specification chiefly relied upon by Genentech and by the district court, column 7, lines 29-59, does not describe in any detail whatsoever how to make hGH using cleavable fusion expression. For example, no reaction conditions for the steps needed to produce hGH are provided; no description of any specific cleavable conjugate protein appears. The relevant portion of the specification merely describes three (or perhaps four) applications for which cleavable fusion expression is *generally* well-suited and then names an enzyme that might be used as a cleavage agent (trypsin), along with sites at which it cleaves ("arg-arg or lys-lys, etc.").[1] Thus, the specification does not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work.

Notwithstanding this limited disclosure, Genentech argues (and the district court found) that those of ordinary skill in the art would have been able to practice the claimed invention without undue experimentation. Essentially, Genentech's argument is that the knowledge of one skilled in the art was sufficient to provide all of the missing information and, more specifically, that the disclosure of a DNA encoding hGH, when combined with prior art cleavable fusion expression techniques applied to non-human proteins, would enable the practice of the claimed method. In support of this argument, Genentech points to the testimony of Dr. Ravetch, who testified as to the knowledge of one skilled in the art, to the extensive description of enzymes in the reference textbook *Methods in Enzymology*, and to the specification's explicit reference to British Patent 2008123-A, which more fully details the potential use of trypsin in cleavable fusion expression.

In response to these arguments, Novo asserts that at the time of filing, trypsin and other like enzymes were used only to digest proteins, not to specifically and precisely cleave conjugate proteins to yield intact, useful proteins, and that the British patent explicitly indicates that trypsin would not be useful for the cleavable fusion expression of arginine-containing proteins such as hGH. Novo further argues that neither the specification nor the references cited by Genentech suggest a single amino acid sequence, out of the virtually infinite range of possibilities,

[1] At column 7, lines 52-58, the specification states: "At least in the latter three applications [of the four applications that are disclosed], the synthetic adaptor molecular [sic] employed to complete the coding sequence of the mRNA transcript can additionally incorporate codons for amino acid sequences specifically cleavable, as by enzymatic action. For example, trypsin will cleave specifically at arg-arg or lys-lys, etc."

that would yield hGH in a useful form when cleaved from the conjugate protein.

We agree with Novo. Genentech's arguments, focused almost exclusively on the level of skill in the art, ignore the essence of the enablement requirement. Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. That requirement has not been met in this specification with respect to the cleavable fusion expression of hGH.

[2] It is true, as Genentech argues, that a specification need not disclose what is well known in the art. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

[3] The specification indicates that it purports to solve a problem. That problem is summarized at column 3, line 65, through column 4, line 8:

> [A] need has existed for new methods of producing hGH and other polypeptide products in quantity and that need has been particularly acute in the case of polypeptides too large to admit to organic synthesis or, for that matter, microbial expression from entirely synthetic genes. Expression of mammalian hormones from mRNA transcripts . . . has permitted only microbial production of bio-inactive conjugates from which the desired hormone could not practically be cleaved.

The problem thus was the difficulty of obtaining hGH from a precursor containing added protein material. This problem was solved by the description of a method of obtaining hGH unaccompanied by a leader sequence or other extraneous proteins, as claimed in the '980 patent. However, the specification for the '199 patent, which is the same as the specification for the '980 patent, does not provide a specific enabling disclosure concerning what the new claim recites, *viz.*, obtaining hGH by cleaving an hGH-containing conjugate protein. That was the problem avoided by the invention claimed in the '980 patent. The present specification contains no more disclosure than the '980 specification, but this patent now purports to claim the unresolved problem that the '980 patent overcame. Genentech is attempting to bootstrap a vague statement of a problem into an enabling disclosure sufficient to dominate someone else's solution of the problem. This it cannot do.

Genentech's arguments in favor of enablement are unavailing. While Genentech's witness, Dr. Ravetch, did state that it would have been possible for a skilled artisan to create a DNA sequence coding for arg-arg-hGH or lys-lys-hGH, he did not discuss the experimentation needed for the creation of DNA coding for more extensive sequences, such as those that have proved necessary to the production of hGH via cleavable fusion expression. Likewise, the description of a wide range of enzymes in *Methods in Enzymology*, by itself, does not render routine the determination of an enzyme-conjugate protein combination. Rather, as Novo argues and the record reflects, various combinations of conjugate protein sequences, cleaving enzymes, and reaction conditions needed to be studied to establish a process for producing hGH in useful form. Finally, the British patent cited in the specification actually works against Genentech's position by explicitly teaching that trypsin would not work well to produce hGH. The specification does not even acknowledge any of the known difficulties associated with using trypsin on an hGH conjugate protein. This specification is so lacking with respect to the limitation of paragraph (b) of claim 1 that providing testimony regarding the skill in the art has been an exercise in futility.

[4] The limited testimony regarding the knowledge of one skilled in the art offered by

Genentech at the preliminary injunction hearing, and relied upon by the district court, is further undermined by the fact that no one had been able to produce *any* human protein via cleavable fusion expression as of the application date. If, as Genentech argues, one skilled in the art, armed only with what the patent specification discloses (a DNA sequence encoding a human protein, in this case, hGH, and a single example of an enzyme and its cleavage site), could have used cleavable fusion expression to make a human protein without undue experimentation, it is remarkable that this method was not used to make any human protein for nearly a year, *see* Shine *et al.*, 285 Nature 456 (June 1980), or to make hGH for five years. *See* Belagaje *et al.*, 3 DNA 120 (1984). Certainly, DNAs encoding desirable human proteins were known at the time of filing (*e.g.*, insulin, described in the British patent), and a great many researchers were attempting to produce human proteins using recombinant DNA technology. This failure of skilled scientists, who were supplied with the teachings that Genentech asserts were sufficient and who were clearly motivated to produce human proteins, indicates that producing hGH via cleavable fusion expression was not then within the skill of the art. The contrary testimony offered by Genentech's witnesses, who hypothesized about the skill of the art more than fifteen years earlier, does not demonstrate the incorrectness of Novo's arguments. *See In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("[A]n expert's opinion on the ultimate legal issue [of enablement] must be supported by something more than a conclusory statement.").

Moreover, it stands to reason that if the disclosure of a useful conjugate protein and the method for its cleavage were so clearly within the skill of the art, it would have been expressly disclosed in the specification, and in the usual detail. Patent draftsmen are not loath to provide actual or constructive examples, with details, concerning how to make what they wish to claim. In addition, as indicated above, the specification of this patent was clearly drafted to claim the invention of obtaining hGH *unaccompanied by* extraneous protein, the cleavage of which was identified by the specification as a problem in this field. Genentech's inventors knew how to enable that which they had invented. These facts underline the inadequacy of the specification in enabling that which it provided only a means to avoid.

The record does not support the district court's implicit finding that the disclosure of trypsin and its cleavage site enables the production of any conjugate protein from which hGH can practically be cleaved and thus produced in useful form; the record indicates that determination of these features required further undue experimentation. None of the expert testimony relied upon by Genentech or by the district court suggests otherwise.[4] Where, as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching. Genentech has not shown that the '199 patent provides that teaching.

Under the circumstances, we are compelled to conclude that the district court made an error of law in ruling that Genentech showed a likelihood of success on enablement. *See In re Epstein*, 32 F.3d 1559, 1568, 31 USPQ2d 1817, 1823 (Fed. Cir. 1994) ("[E]nablement is a question of law . . . which may involve subsidiary questions of fact."). Furthermore, since we are able to review the record and to read the specification, there is no reason why we should limit our decision here to reversing the grant of the preliminary injunction. Rather, because the parties agreed at oral argument that the enablement issue had been thoroughly ventilated by the extensive arguments before the district court and that court's extensive analysis,[5] we deem it appropriate to rule on the merits of Novo's defense of invalidity. *See* 28 U.S.C. § 2106 (1994) ("The Supreme Court or any other court of appellate jurisdiction may . . . direct the entry of such appropriate judgment, decree, or order, or require such further proceedings to be had as may be just under the circumstances."); *Chicago Observer, Inc. v. City of Chicago*, 929 F.2d 325, 329 (7th Cir. 1991) (reversing preliminary injunction and instructing district court to enter judgment in favor of defendant because the plaintiff "has not suggested that it holds more evidence it could offer at trial and we cannot imagine what additional evidence could aid its cause. Litigation is costly not only for the litigants but also for parties in other cases waiting in the queue for judicial attention. Once it becomes clear that additional proceedings are pointless, the court should bring the case to a close."). We therefore hold that claim 1 and hence the '199 patent are invalid as a matter of law for failure of the specification to enable the practice of the claimed method.

Novo has also argued that the '199 patent is invalid for lack of a written description of the claimed invention and that it is not infringed by Novo. Given our decision on the enablement question, we need not reach these issues.

B. *Other Factors*

Novo also challenges the district court's findings that irreparable harm, the equities, and the public interest favored Genentech. In view of our conclusion concerning the invalidity of the '199 patent, we need not consider these other findings.

CONCLUSION

The court abused its discretion by granting the preliminary injunction based upon an error of law. The district court's error was in finding that Genentech had shown a likelihood of success on the merits since the '199 patent is invalid for failure of the specification to meet the enablement requirement of § 112, ¶ 1. Accordingly, we vacate the injunction and instruct the district court to dismiss Genentech's claim for infringement of the '199 patent on the ground that the patent is invalid.

VACATED.

[4] Novo's witness, Dr. Villa-Komaroff, merely stated on cross-examination that, assuming arg-arg-hGH was initially produced and successfully extracted from the transformed cell, that "[u]nder the best condition, approximately five percent of the time there will be in the [post-digestion] mix [hGH]." This statement, characterized by Genentech as an admission, was made in the limited context of partial trypsin digests of isolated arg-arg-hGH, but none of the necessary experimentation is described in the specification, which is where it should be if it is to contribute to an enabling disclosure.

[5] Genentech stated that it would introduce new evidence at a full trial only in response to new arguments and new defenses raised by Novo. Novo revealed that it had no intention of raising any new arguments or defenses, stating that the "full and complete record" on appeal gave this court "the benefit of everything it really needs" to reach ultimate issues of validity. Thus, considerations that would normally dictate that we limit our decision to reversing the grant of the preliminary injunction are not present. *See University of Texas v. Camenisch*, 451 U.S. 390, 395 (1981) (stating that it is generally inappropriate to render a final judgment on the merits at the preliminary injunction stage because "a preliminary injunction is customarily granted on the basis of procedures that are less formal and *evidence that is less complete than in a trial on the merits.*") (citations omitted) (emphasis added).

U.S. District Court
District of Columbia

U.S. v. The Thomson Corp.

No. 96-1415 (PLF)

Decided December 23, 1996

COPYRIGHTS

1. Elements of copyright — Statutory Elements — Originality (§205.0707)

Legal publisher asserting copyright in "star pagination" of its case law reporters has "thin" copyright claim at best, since in order to prevail, publisher would have to demonstrate that its reporter page numbers and their placement themselves represent original, creative decision about selection or arrangement, since where and on what pages text of court opinion appears does not embody any original creation of compiler, and since star pagination does not in any way take advantage of that part of publisher's effort in making compilation that reflects its intellectual effort, and instead simply reflects accident of where particular portion of opinion ended up in reporter.

2. Rights in copyright; infringement — Ownership of copyright — Transfer and licensing (§213.0310)

Provision in proposed final judgment in antitrust action, by which two legal publishing companies, as condition of their merger, would be required to grant license for fee to anyone who wants to "star paginate" to case law reporter system, is not in public interest as required by Antitrust Procedures and Penalties Act, 15 USC 16, since copyrightability of star pagination is questionable at best, since including star pagination license in final judgment might be construed as government's endorsement of publishers' dubious copyright claim, since provision would legitimize publishers' ability to profit from licenses while copyright issue is litigated, and since that fact alone is troublesome in view of weakness of copyright claim and limited market power of many of those who would have to pay license fee.

Action brought under federal antitrust laws by the United States and by states of California, Connecticut, Illinois, Massachu-

Amdt 35/H (NE) Linda 4/24/02

EXPEDITED PROCEDURE - EXAMINING GROUP 1645

S/N 09/077,572 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael A. Apicella et al.	Examiner: S. Devi	
Serial No.:	09/077,572	Group Art Unit: 1645	
Filed:	October 13, 1998	Docket: 875.001US2	
Title:	NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA		

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.116

copy of paper # 30

Box AF
Commissioner for Patents
Washington, D.C. 20231

In response to the final Office Action mailed February 21, 2001, Applicant respectfully requests that the Examiner consider and enter the following amendments and remarks in connection with the above-identified patent application.

This response id accompanied by an Appeal Brief.

IN THE SPECIFICATION

Please delete the paragraph beginning on page 13 at line 27 and ending on page 14 at line 7, and insert the following paragraph therefor:

--Two plasmids, termed pB28 and pB29, each with a mini-Tn3 transposon containing the chloramphenicol acetyltransferase (CAT) gene inserted into the *htrB* open reading frame at a different location. Nontypeable *Haemophilus influenza* strains 2019 B28 and 2019 B29 were deposited on November 14, 2000 with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 under the provisions of the Budapest Treaty, and all restrictions will be irrevocably removed upon the granting of a patent on this application. Strain B28 has been accorded accession number PTA-2667 and strain B29 has been accorded accession number PTA-2668. Each plasmid was used to transform nontypeable *H. influenzae* strain 2019 and bacterial cell transformants were selected for by growth in the presence of chloramphenicol (1.5 μg/ml), resulting in identification of mutant strains designated NTHi B28 and B29, respectively. Locations of the mTn3 insertion in the chromosomes of the NTHi mutants were confirmed by genomic Southern hybridization using the 2.4 kb *Bgl*II fragment as a probe. In particular, a *Bgl*II digest of NTHi strain 2019 DNA resulted in a 2.4 kb fragment; whereas

similar digests of DNA from mutants NTHi B28 and B29 revealed 4.0 kb fragments. Further, the 4.0 kb fragments were digested by *Eco*RI which is present in the mTn3.--

A clean copy of this paragraph is attached hereto.

IN THE CLAIMS

Please substitute the claim set in the appendix entitled Clean Version of Pending Claims for the previously pending claim set. Specific amendments to individual claims are detailed in the following marked up set of claims.

Please add new claim 34 and amend the claims as follows.

22. (Amended) A method of making a mutant endotoxin comprising

mutating an htrB gene encoding a wild type endotoxin in [within] a wild type gram-negative bacterial pathogen to provide the mutant endotoxin; wherein the mutant endotoxin is the same as the wild type endotoxin except for [form an htrB mutant pathogen, wherein the htrB gene encodes an endotoxin] lacking one or more secondary acyl chains of lipid A [contained in a wild type gram-negative bacterial pathogen and lacking 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen], and wherein the mutant endotoxin has substantially reduced toxicity when compared to the endotoxin of the wild type gram-negative bacterial pathogen[, and

purifying the mutant endotoxin from the htrB mutant pathogen].

29. (Amended) A method for producing endotoxin-specific antisera, the method comprising

(a) immunizing an individual with a vaccine formulation comprising an htrB mutant of a gram-negative bacterial pathogen, endotoxin isolated from the htrB mutant of the gram-negative bacterial pathogen, or endotoxin purified from the htrB mutant of the gram-negative bacterial pathogen wherein the endotoxin is conjugated to a carrier protein; and

(b) collecting antibody produced from the immunized individual;

wherein the htrB mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A [lacks one or more secondary acyl chains of lipid A contained in a wild type gram-negative bacterial pathogen and lacks 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen resulting in substantially reduced toxicity when compared to lipid A of the wild type gram-negative bacterial pathogen].

34. (New) The method of claim 22, further comprising the step of purifying the mutant endotoxin.

REMARKS

A. Status of Claims

Reconsideration of this application as amended is requested. Claims 22 and 29 having been amended, claim 34 being newly added, claims 22-26, 29 and 32-34 are pending. No new subject matter has been added.

The amendments to the claims are fully supported by the specification as originally filed. The amendments are made to clarify the claims, and are not intended to limit the scope of equivalents to which any claim element may be entitled. Support for new claim 34 is found in previously pending claim 22. Support for the amendments to claims 22 and 29 is found throughout the specification. One having ordinary skill in the art upon reading the full disclosure would recognize that the claimed mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A, *i.e.*, only one change is made between the wild type and mutant endotoxin, and that change is the number of acyl chains in the lipid A. For example, Figure 1 depicts a wild type endotoxin (hexaacyl), and Figures 2A and 2B depict mutant endotoxin (pentaacyl and tetraacyl, respectively). *See also* Brief Description of the Figures on page 4 of the specification. The only change between Figure 1 and Figures 2A/2B is a decrease in the number of secondary acyl chains. There is no other change in the lipid A (such as length of the remaining chains). Further, page 4, lines 3-9 of the specification states that the lipid A produced by the mutant lacks one or both of the fatty acids, thereby rendering the endotoxin substantially reduced in toxicity, and yet retaining antigenicity as compared to wild

type. Page 7, lines 7-10 states that the mutants specifically lack one or more secondary acyl chain fatty acids that are ester-bound to the hydroxyl grous of two of the four molecules of β-OH. Moreover, on page 13, lines 1-5 of the specification states that the lipid A structure of the mutant endotoxin has one or two fewer acyl chains than the wild type.

It should be noted that "adequate description under the first paragraph of 35 U.S.C. §112 does not require *literal* support for the claimed invention." (emphasis in original) *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat App. 1993) (copy enclosed); *citing In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979) (copy enclosed); *In re Edwards*, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978) (copy enclosed); *In re Werthein*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) (copy enclosed). Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an applicant had possession of the concept of what is claimed. *In re Anderson,*, 471 F.2d 1237, 176 USPQ 331, 333 (CCPA 1973) (copy enclosed). As discussed above, one with ordinary skill in the art upon reading the full specification would understand that the claimed mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A Therefore, the claims as currently amended are fully supported by the specification, and thus comply with the adequate description requirement of 35 U.S.C. §112, first paragraph.

B. Rejections of Claims under 35 U.S.C. §112, First Paragraph

1. Deposit of Microorganisms

The Examiner has maintained the rejection of claims 22-26 and 29 under 35 U.S.C. § 112, first paragraph. The Examiner acknowledges that Appellants have submitted a copy of the ATCC deposit receipt showing that the proper strains have been deposited under the provisions of the Budapest Treaty and provided the proper statement that all restrictions will be irrevocably removed upon the granting of a patent in compliance with 37 CFR 1.801-1.809. The Examiner, however, maintained the enablement rejection because Appellants in advertently provided the incorrect location in the specification into which the deposit information was to be inserted. Applicants have now indicated the correct location where the deposit information is to be inserted into the specification. Therefore, this rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

2. Written Description

The Examiner has rejected claims 22-26, 29, 32 and 33 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. In particular, the Examiner objected to the phrase "lacking 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen". Applicant has now amended the claims to delete this phrase. Therefore, this rejection is rendered moot, and should be withdrawn.

C. Non-Statutory Double Patenting Rejection

The Examiner provisionally rejected the pending claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 23, 25 and 29 of U.S. Patent Application No. 08/565,943. Applicants will consider filing a terminal disclaimer upon notification of otherwise allowable subject matter. A terminal disclaimer may not be appropriate once the scope of allowable claims is determined in the present application, and dependent upon which application is allowed first.

D. Objection to the Drawings

Corrected formal drawings will be submitted upon notification of allowance of the claims.

E. Distinction of Pending Claims over Previously-Cited Art

1. Karow et al. and Westphal et al.

The pending claims are distinguishable over Karow et al., (*Journal of Bacteriology* 174:7407-7418) in view of Westphal et al. (*Methods Carbonydr. Chem.* 5:83-91, 1965).

The claims as amended recite a method of making a mutant endotoxin, wherein the mutant endotoxin *is the same as* the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A This is clearly distinguishable over Karow et al.

The inventors obtained a culture of the *E. coli htrB* mutant (hereinafter "the Karow strain" or "the Karow mutant") from Costa Georgopoulos, one of the co-authors of the cited

Karow *et al.* article. June 30, 2000 Declaration of Drs. Gibson and Apicella under 37 C.F.R. § 1.132 (hereinafter "§132 Declaration"), ¶ 8. The inventors then performed studies on the lipid A made by the mutant strain. In particular, they performed a mass spectrometric examination of the Karow strain. The results of this examination clearly showed that the Karow strain had a set of lipid A structures different in very important ways from the *htrb* mutant pathogens of the present invention.

The Karow mutant makes a set of lipid A structures different from the mutants of the present invention. First, the Karow culture made a fully hexaacylated lipid A structure. §132 Declaration, ¶ 8. A hexaacylated lipid A structure is not covered by the pending claims, as hexaacylated lipid A has the same number of secondary acyl chains on the lipid A as the wild type endotoxin rather than "lacking at least one secondary acyl chain on lipid A" as recited by the claims. Second, the Karow mutant made an endotoxin containing fewer than six acylated lipid A fatty acids but additionally had changes in the length of the other fatty acid chains. *Id.* For example, the Karow *et al.* mutant contained a mixture of new unsaturated fatty acids, most likely palmitoleic (C16:1) in place of the single lauric acid (C12:0) fatty acid. *Id.* The lipid A species of the present invention does not contain these changes; the mutant endotoxin of the present invention is the same as the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A. Therefore, significant differences exist in the lipid A structures in the *htrB* gene deletion mutants of the present invention as compared to the various lipid A structure made by Karow's strain.

The Westphal *et al.* reference does not remedy the deficiencies of Karow *et al.* Westphal *et al.* disclose a method of purifying Gram negative bacterial lipopolysaccharides by phenol-water extraction. They do not, however, teach or suggest the present method of purifying the endotoxin recited by the present claims, as they did not possess this endotoxin. Therefore, the present invention is not obvious over Karow et al. in view of Westphal et al.

2. Karow et al. in view of Westphal et al. and Gupta et al.

The pending claims are distinguishable over Karow et al., (*Journal of Bacteriology* 174:7407-7418) in view of Westphal et al. (*Methods Carbonydr. Chem.* 5:83-91, 1965), and further in view of Gupta et al. (Infect. Immun. 60: 3201-3208, 1992).

Karow et al. and Westphal et al. have been discussed above. Gupta et al. does not remedy the deficiencies of Karow et al. and Westphal et al. Gupta et al. disclose the conjugation of chemically-modified LPS to cholera toxin and other proteins. They do not, however, teach or suggest a method of making a mutant endotoxin, wherein the mutant endotoxin is the same as the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A.

Therefore, the present invention is not obvious over Karow et al. in view of Westphal et al. and Gupta et al.

CONCLUSION

Applicant believes that all claims are in condition for allowance. Reconsideration of the rejections of the claims and allowance of all the claims is respectfully requested. The Examiner is invited to contact the Applicant's attorney if prosecution of the present application can be assisted thereby.

Please charge any required fees to Deposit Account No. 19-0743.

Respectfully submitted,

MICHAEL A. APICELLA ET AL.

By their Representatives,

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Date 15 October 2001 By _____

Ann S. Viksnins
Reg. No. 37,748

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 15th day of October, 2001.

Name Candis B. Buending

Signature _____

years' worth of license fees, or $1,260, since the date of its first letter to defendants on September 23, 1933 informing them that they were required to sign a license agreement. By imposing the statutory minimum of $500 per number of works infringed,[1] defendants will be required to pay $11,500, approximately nine times the amount defendants would have paid in licensing fees. This Court finds that to be an appropriate penalty for the defendants' infringements.

Finally, the Copyright Act provides that the court "in its discretion may allow the recovery of full costs [and] may also award a reasonable attorney's fee to the prevailing party as part of the costs." 17 U.S.C. § 505. In order to encourage suits to redress copyright infringement, attorney fees are awarded to a prevailing plaintiff as a matter of course. *Frost Belt Int'l Recording Enterprises, Inc. v. Cold Chillin' Records*, 758 F.Supp. 131, 140 (S.D.N.Y. 1990) The award of attorney's fees is the rule rather than the exception. *Micromanipulator Co. v. Bough*, 779 F.2d 255, 259 [228 USPQ 443] (5th Cir. 1985). Consequently, this Court finds plaintiffs entitled to reasonable attorney's fees for the prosecution of this action.

The declaration of Marjorie R. Esman submitted by plaintiffs states that plaintiffs incurred $1,747.00 in attorney's fees for services, including: preparation and service of discovery materials, participation in a scheduling conference; preparation of and filing of a witness and exhibit list; preparation and filing of the motion for summary judgment. The declaration states that plaintiffs incurred costs and expenses in the amount of $485.37 for filing of the complaint, payments to the process server, reasonable photocopies, and long distance telephone charges. This Court finds these declared attorneys's fees, costs and expenses to be reasonable.

Conclusion

For the reasons set forth above,

IT IS ORDERED that plaintiffs' motion for summary judgment is hereby GRANTED in all respects except plaintiffs' request for statutory damages in the amount of $2,500 per claim of infringement. Accordingly, defendants are liable to plaintiffs in the amount of $11,500 in statutory damages for copyright infringements, $1,747.00 in attorney's fees, and $485.37 in costs and expenses. Judgment will be so entered.

[1] See *Frank Music Corp. v. Metro-Goldwyn-Mayer Inc.*, (9th Cir.), 886 F.2d 1545 [12 USPQ2d 1412], *cert. den'd* 110 S.Ct. 1321, 494 U.S. 1017 (1989) which states that the number of works infringed is the appropriate calculation for statutory damages and not the number of infringements. The affidavit of James Hutcherson, investigator for BMI, lists 23 works which were infringed on July 11, 12, 18, and 19, 1992.

U.S. Patent and Trademark Office
Board of Patent Appeals and Interferences

Ex parte Parks

No. 93-2740

Decided September 2, 1993
Released January 4, 1994

PATENTS

1. Practice and procedure in Patent and Trademark Office — Reissue — Broader claims sought (§110.1313)

Patentability/Validity — Specification — Written description (§115.1103)

Claims in reissue application for method of determining nitrogen content of sample were improperly rejected on ground of inadequate descriptive support under 35 USC 112, first paragraph, since originally-filed disclosure need only convey, to one of skill in art, that applicant had possession of concept of what is claimed in order to satisfy description requirement, since lack of literal basis in disclosure for limitation that decomposition step of claims be "conducted in the absence of a catalyst" thus does not establish prima facie case for lack of descriptive support, and since it cannot be held that originally-filed disclosure would not have conveyed concept of effecting decomposition at elevated temperature in absence of catalyst.

2. Practice and procedure in Patent and Trademark Office — Reissue — Broader claims sought (§110.1313)

Claims in reissue application for method of determining nitrogen content of sample are overbroad under 35 USC 251, since application was filed more than two years after grant of original patent, since any claim which does not contain negative limitation expressly excluding presence of catalyst in decomposition step of method is broader than original claims, and since claims in question do not accomplish such exclusion by reciting phrase "consisting essentially of" in characterizing decomposition step.

Particular patents — Chemical — Nitrogen detection

4,018,562, Parks and Marietta, chemiluminescent nitrogen detection apparatus and method, claims 81-93 in application for reissue rejected.

Appeal from final rejection of claims in application for reissue of patent (Jill Johnston, primary examiner).

Application of Robert E. Parks and Robert L. Marietta, serial no. 708,810, filed May 31, 1991, continuation of serial no. 340,540, filed April 18, 1989 and abandoned, for reissue of patent no. 4,018,562, granted April 19, 1977 on application serial no. 625,510, filed Oct. 24, 1975 (chemiluminescent nitrogen detection apparatus and method). From final rejection of all claims in application, applicants appeal. Rejection of claims 1-10, 20-22, 55-80, and 94-106 reversed; rejection of claims 81-93 affirmed.

Before Calvert, vice chairman, and Steiner and Tarring, examiners-in-chief.

Steiner, examiner-in-chief.

This is an appeal from the final rejection of claims 1 through 10, 20 through 22 and 55 through 106, all the claims in this application for reissue of Patent No. 4,018,562 (the '562 patent).

THE INVENTION

The claimed invention is a method for determining the nitrogen content of a sample comprising manipulative steps which include decomposing the sample in an oxygen/inert gas atmosphere at an elevated temperature to obtain nitric oxide and causing the generated nitric acid to undergo a chemiluminescent reaction with ozone.

Claims 1, 81 and 94 are illustrative and read as follows:

1. The method for determining the total chemically combined nitrogen content of a sample comprising the steps:

a. decomposing said sample in one step in the presence of an oxygen-rich atmosphere of oxygen and an inert gas and at a temperature sufficiently above 700°C. that substantially all of the chemically bound nitrogen is recovered as nitric oxide (NO), such decomposition being conducted in the absence of a catalyst,

b. causing the nitric oxide produced by such decomposition to undergo a chemiluminescent reaction with ozone, and

c. determining the magnitude of the chemiluminescent reaction to indicate the quantity of chemically combined nitrogen in said sample.

81. A method for determining the total chemically combined nitrogen content of a sample, said method comprising the steps of:

(a) decomposing said sample in one step, said decomposing step consisting essentially of decomposing said sample in the presence of an oxygen-rich atmosphere of oxygen and an inert gas and at a temperature sufficiently above 700°C that substantially all of the chemically bound nitrogen is recovered as nitric acid (NO);

(b) causing the nitric oxide produced by such decomposition to undergo a chemiluminescent reaction with ozone; and

(c) determining the magnitude of the chemiluminescent reaction to indicate the quantity of chemically combined nitrogen in said sample.

94. A method for determining the total chemically combined nitrogen content of a sample, said method comprising the steps of:

(a) decomposing said sample in one step in the presence of an oxygen-rich atmosphere of oxygen and an inert gas and at a temperature sufficiently above 700°C that substantially all of the chemically bound nitrogen is recovered as nitric oxide (NO) according to the formula:

$$R\text{-}N + O_2 \triangleright CO_2 + H_2O + NO$$

(b) causing the nitric oxide produced by such decomposition to undergo a chemiluminescent reaction with ozone; and

(c) determining the magnitude of the chemiluminescent reaction to indicate the quantity of chemically combined nitrogen in said sample.

THE REJECTIONS

Claims 1 through 10, 20 through 22 and 55 through 80 stand rejected under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support. Claims 81 through 106 stand rejected under 35 U.S.C. 251 in that they are broader than the originally patented claims.[1] In addition, all the

[1] The ultimate paragraph of 35 U.S.C. 251 reads as follows:

No reissued patent shall be granted enlarging the scope of the claims of the original patent unless applied for within two years from the grant of the original patent.

appealed claims stand rejected under 35 U.S.C. 251 for lack of the requisite "error."

The rejection under the first paragraph of 35 U.S.C. 112, the rejection of claims 94 through 106 under 35 U.S.C. 251 as broader than the original claims, and the rejection of all the appealed claims under 35 U.S.C. 251 for lack of the requisite "error" are reversed; the rejection of claims 81 through 93 under 35 U.S.C. 251 as broader than the original claims is affirmed.

OPINION

The Rejection of Claims 1 through 10, 20 through 22 and 55 through 80 under the first paragraph of 35 U.S.C. 112.

The initial burden of establishing a *prima facie* basis to deny patentability to a claimed invention on any ground is always upon the examiner. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In rejecting a claim under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support, it is incumbent upon the examiner to establish that the originally-filed disclosure would not have reasonably conveyed to one having ordinary skill in the art that an appellant had possession of the now claimed subject matter. *Wang Laboratories, Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993). Adequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention. *In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979); *In re Edwards*, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978; *In re Werthein*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

[1] The examiner contends that the rejected claims lack adequate descriptive support because there is "no literal basis for the"[2] claim limitation "in the absence of a catalyst." Clearly, the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112. *In re Herschler, supra; In re Edwards, supra; In re Wertheim, supra.*

The examiner notes that in *Parks v. Fine*, 773 F.2d 1577, 227 USPQ 432 (Fed. Cir. 1985), involving the claimed subject matter, the limitation "in the absence of a catalyst" was considered material. Suffice it to say, no issue under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support for the limitation "in the absence of a catalyst" was before the court.

We are not unmindful of the decision in *Ex parte Grasselli*, 231 USPQ 393 (Bd.App. 1983) *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984), which involved claims to a process for the ammoxidation of propane or isobutane employing a catalyst "free of uranium and the combination of vanadium and phosphorus." Under the particular facts in that case, it was held that the negative limitation introduced new concepts in violation of the description requirement of the first paragraph of 35 U.S.C. 112, citing *In re Anderson, supra*. In the situation before us,[3] it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art that appellants had possession of the *concept* of conducting the decomposition step generating nitric acid in the absence of a catalyst. See, for example, column 5 of the '562 patent, first paragraph, wherein FIG. 4 is discussed. Pyrolysis temperatures of between 600°C and 700°C, and above 700°C were employed to achieve conversion of chemically bound nitrogen to nitric oxide. Smooth conversion was obtained above 700°C, while the optimum conversion was found to occur above 900°C. Throughout the discussion which would seem to cry out for a catalyst if one were used, no mention is made of a catalyst.[4]

Moreover, according to two declarations by Wentworth, a professor of chemistry at the University of Houston, whose expertise in this particular art has not been challenged, one having ordinary skill in the art would have recognized that the reaction generating nitric oxide, according to the equation disclosed in the '562 patent, is conducted without a catalyst. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Lemin*, 364 F.2d 864, 150 USPQ 546 (CCPA 1966). Thus, it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art the concept of effecting decomposition at an elevated temperature in the absence of a catalyst. *In re Anderson, supra.*

Accordingly, the examiner's rejection of claims 1 through 10, 20 through 22 and 55 through 80 under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support is reversed.

The Rejection of Claims 81 through 106 under 35 U.S.C. 251 as Broader than the Original Claims.

We initially observe that on page 6 of the Brief,

> appellants agree that any claim in the reissue application that does not contain a limitation that *means* "in the absence of a catalyst" is broader than original claims 1–10 and hence unpatentable under 35 USC 251 (appellants' emphasis).

Claims 81 through 106 do not contain a negative limitation which expressly precludes the presence of a catalyst. However, appellants contend that claims 81 through 93 exclude the presence of a catalyst by virtue of the phrase "consisting essentially of" in characterizing the decomposition step, and that claims 94 through 106 exclude the presence of a catalyst by virtue of the recited equation for the decomposition reaction, which equation does not reflect the presence of a catalyst.

[2] In our opinion, the phrase "consisting essentially of," as employed in claims 81 through 93, limits decomposition to a single step and, in that sense, is redundant since decomposition is performed "in one step." However, it is not apparent and appellants have not explained why the expression "consisting essentially of" excludes the presence of a catalyst during the recited decomposition step.[5] It would, therefore, appear that claims 81 through 93 are broader than original claims 1 through 10 and, hence, were properly rejected by the examiner under 35 U.S.C. 251. Accordingly, the examiner's rejection of claims 81 through 93 under 35 U.S.C. 251 is affirmed.

Claims 94 through 106 recite the decomposition reaction in a manner which, according to the Wentworth declarations, means that no catalyst was employed. *In re Lemin, supra.* Accordingly, claims 94 through 106 would not appear broader than original claims 1 through 10 and, hence, the examiner's rejection of claims 94 through 106 under 35 U.S.C. 251 is reversed.

The Rejection of the Appealed Claims Under 35 U.S.C. 251 for Lack of the Requisite Error.

This rejection is reversed essentially for the reasons advocated by appellants on appeal. We emphasize that the practice of submitting claims as a hedge against the possible invalidity of original claims has been judicially sanctioned. See, for example, *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 882 F.2d 1556, 11 USPQ2d 1750 (Fed. Cir. 1989); *In re Altenpohl*, 500 F.2d 1151, 183 USPQ 38 (CCPA 1974); *In re Handel*, 312 F.2d 943, 136 USPQ 460 (CCPA 1963).

In summary, the examiner's rejection of claims 81 through 93 is affirmed; the rejection of claims 1 through 10, 20 through 22, 55 through 80 and 94 through 106 is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR 1.136(a). See the final rule notice, 54 F.R. 29548 (July 13, 1989), 1105 O.G. 5 (August 1, 1989).

AFFIRMED-IN-PART.

U.S. Patent and Trademark Office
Board of Patent Appeals and Interferences

Ex parte Heymes

No. 93-1646

Decided November 9, 1993
Released January 4, 1994

PATENTS

1. Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§115.0903.03)

Patentability/Validity — Obviousness — Secondary considerations generally (§115.0907)

Application claims for chemical compounds were properly rejected as obvious under 35 USC 103, since claims are prima facie obvious in view of cited references, since record does not show that claimed compounds, which are intermediates to patented compounds having antibiotic properties, have no known utility other than as

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[1] See page 4 of the Answer, second full paragraph, line 4, and page 7 thereof, last two lines.

[2] Whether the requirement for an adequate written description has been met is a question of fact and, hence, driven by the exigencies of each case. *Wang Laboratories, Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993).

[3] A "catalyst" normally functions to accelerate a particular reaction. See for example, Hawley, *Condensed Chemical Dictionary*, Tenth Edition, 1981, pp. 205 and 206, copies of which are enclosed for appellants' convenience and made of record.

[4] Compare *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805, 812, note 6 (Fed. Cir. 1986).

mor finds abuse of discretion in this case because it asserts that the excluded questions were necessary both to establish the basis for Whitney's "conclusory" opinions and to prove their error. See Fed.R.Evid. 705.

[4] We find no manifest error in Judge Bonsal's contrary determination. Armor's attempt at cross-examination was not properly an attempt to elicit the "basis" of Whitney's testimony. Whitney explicitly testified on direct examination that his opinion was *based* on a reading of the claims and the specifications together. It is evident that Armor questioned Whitney's assumption that the specifications were relevant, but this disagreement was on a point of law, which could be argued separately to the judge, and which was not a proper subject for witness testimony. Marx & Co. v. Diners' Club, supra, 550 F.2d at 509-10. Moreover, the *fact* that there was a literal correspondence — if it was a fact — could easily be determined by the Judge himself. Protracted questioning could thus properly be limited under Rule 403 as a waste of time.

[5,6,7] Although Armor has not directly challenged Judge Bonsal's decision on the merits of this case, it is part of Armor's argument that the court's refusal to permit further questioning on the literal correspondence of terms reveals a misapprehension by the court of the legal standards to be applied. We think, on the contrary, that Armor's understanding of the law is in error. The "doctrine of equivalents" which governs determinations of infringement requires an assessment of function rather than form in measuring the claims of a patent. As this court said in Triax Co. v. Hartman Metal Fabricators, 479 F.2d 951, 958, 178 USPQ 142, 147 (2d Cir.), cert. denied, 414 U.S. 1113, 180 USPQ 97 (1973): "The broadly stated test, enunciated in Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 608, 70 S. Ct. 854, 94 L. Ed. 1097, 85 USPQ 328, 330 (1950), quoting Sanitary Refrigerator Co. v. Winters, 280 U.S. 30, 50 S. Ct. 9, 74 L. Ed. 147, 3 USPQ 40 (1929), is whether the challenged device 'performs substantially the same function in substantially the same way to obtain the same result' as the challenging device." In a crowded field such as the elevator art, a literal correspondence of terms may be a starting point for analysis, Decca Ltd. v. United States, 420 F.2d 1010, 1013-14, 164 USPQ 348, 350-352 (Ct. Cl.), cert. denied, 400 U.S. 865, 167 USPQ 321 (1970) see Graver Tank & Mfg. Co. v. Linde Air Products, Co., supra at 607, 85 USPQ at 330, but "mere application of claim phraseology or a word-by-word correspondence is not by itself enough to establish infringement." 7 Deller's Walker on Patents, §510 at 174 (2d ed. 1972) (footnote omitted). And although it is the claim alone which determines the scope of a patent monopoly, claims which are not free from ambiguity may not be interpreted solely according to their "dictionary" meaning, but must be interpreted by reference to the "art or technology to which the claimed subject matter pertains." Application of Salem, 553 F.2d 676, 682-83, 193 USPQ 513, 518 (C.C.P.A. 1977). For that purpose, a court is not precluded from consulting the specifications. MacLaren v. B-I-W Group, Inc., supra, 535 F.2d at 1372, 190 USPQ at 516-517.

In the light of these principles, Armor stood to gain very little, if anything, by its planned line of cross-examination. The judge, who had heard testimony on literal correspondence before, did not abuse his discretion by cutting short an inquiry that would not assist him in his factfinding role.

Because we find no prejudicial error in the conduct of the trial below, we hold that appellants have not been deprived of a "full and fair" hearing on the issues submitted to the court. The judgment confirming the arbitration award is affirmed.

Court of Customs and Patent Appeals

In re Herschler

No. 78-548

Decided Feb. 1, 1979

PATENTS

1. Affidavits — In general (§12.1)

Patent and Trademark Office's physical possession of original affidavit at time of Board of Appeals' decision makes further verification unnecessary.

2. Applicants for patent — In general (§14.1)

Pleading and practice in Patent Office — Rules effect (§54.9)

Inventorship of great-grandparent application was not effectively amended by Patent and Trademark Office's acquiescence in accepting sole inventorship of grandparent, nor was great-grandparent amended nunc pro tunc by submission of copies of Rule 45 papers.

3. Specification — In general (§62.1)

Specification — Claims as disclosure (§62.3)

Specification — Sufficiency of disclosure (§62.7)

Function of description requirement is to ensure that inventor had possession, as of filing date of application relied upon, of specific subject matter later claimed by him; how specification accomplishes this is not material; claimed subject matter need not be described in haec verba to satisfy description requirement; it is not necessary that application describe claim limitations exactly, but only so clearly that one having ordinary skill in pertinent art would recognize from disclosure that applicant invented processes including those limitations.

4. Specification — Sufficiency of disclosure (§62.7)

Written description of class of compounds must provide measure of predictability for utility described for that class.

5. Pleading and practice in Patent Office — Rejections (§54.7)

It is incumbent, in first instance, for Patent and Trademark Office to give reasons why written description is insufficient.

6. Specification — Sufficiency of disclosure (§62.7)

Known steroids, when considered as class of compounds carried through layer of skin by DMSO, is not so large that single example in specification could not describe varied members with their further varied properties.

7. Specification — Sufficiency of disclosure (§62.7)

Court of Customs and Patent Appeals maintains line first clearly drawn in In re Fuetterer, 138 USPQ 217, where it found written description requirement to be satisfied where claims were drawn to rubber stock composition useful in producing tire treads, included recitation of inorganic salt capable of maintaining homogeneous distribution of another component in composition, and disclosure listed function described and four members of class having that function.

8. Claims — Specification must support (§20.85)

Specification — Sufficiency of disclosure (!62.7)

Principles stated in In re Driscoll, 195 USPQ 434, In re Ruschig, 154 USPQ 118, and In re Fried, 136 USPQ 429, concerning application with claims either to intermediate classes of new compounds per se or claims drawn to processes using those new compounds are still alive and well.

9. Specification — Sufficiency of disclosure (§62.7)

Claims drawn to use of known chemical compounds in manner auxiliary to invention must have corresponding written description only so specific as to lead one having ordinary skill in art to that class of compounds; occasionally functional recitation of those known compounds in specification may be sufficient as that description.

10. Patentability — Evidence of — State of art (§51.467)

Papers presented to New York Academy of Sciences could, where there is prima facie showing of obviousness to rebut, if properly presented, indicate wide-scale acceptance in art and provide secondary consideration capable of overcoming 35 U.S.C. 103 rejection.

Particular patents — Tissue Penetration

Herschler, Enhancing Tissue Penetration of Physiologically Active Steroidal Agents with DMSO, rejection of claims 1-5 and 9-13 reversed.

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of Robert J. Herschler, Serial No. 304,283, filed Nov. 6, 1972, division of application, Serial No. 69,155, filed Sept. 2, 1970, continuation-in-part of application, Serial No. 753,231, filed Aug. 16, 1968, continuation-in-part of application, Serial No. 329,151, filed Dec. 9, 1963. From decision rejecting claims 1-5 and 9-13, applicant appeals. Reversed.

Stanley M. Teigland, San Francisco, Calif., for appellant.

Joseph F. Nakamura (Fred W. Sherling and Ernest G. Therkorn, of counsel) for Commissioner of Patents and Trademarks.

Before Rich, Baldwin, and Miller, Associate Judges, and Kashiwa,* and Ford,** Judges.

Baldwin, Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the rejection of claims 1-5 and 9-13 in appellant's application serial No. 304,283,[1] filed November 6, 1972, for "Enhancing Tissue Penetration of Physiologically Active Steroidal Agents with DMSO."[2]

The board affirmed the examiner's rejection of all claims under 35 USC 103 as unpatentable over Lubowe in view of Faust, Marson or Brown. The board also affirmed a rejection, first entered pursuant to its authority under 37 CFR 1.196(b),[3] of each of the claims under 35 USC 102(b) or 103 over Stroughton et al., Stroughton or Kligman.[4] We reverse.

The Invention

The appellant has found that DMSO enhances the penetration of a number of materials through skin tissue. In the application at hand, a mixture of DMSO and a "physiologically active steroidal agent" is administered to skin (or a mucous membrane) with the result that the steroid penetrates the membrane. The claimed process provides such advantages as the elimination of injection by needle and the ability to administer localized doses of the drug without resort to a systemic dose.

Claim 1 is typical of the invention:

> 1. A method of enhancing the penetration into and across an external membrane barrier of a human or animal subject of a physiologically active steroidal agent capable of eliciting a physiological effect upon topical application thereof, which comprises the concurrent topical administration to the external membrane of an amount of said steroidal agent effective to produce the desired physiological effect and an amount of DMSO sufficient to effectively enhance penetration of said steroidal agent to achieve the desired physiological effect.

The Prior Art

The following references were relied upon to support the rejection under §103:

Lubowe Patent No. 2,942,008 issued on June 21, 1960.

Brown et al., "A Note on the Toxicity and Solvent Properties of Dimethyl Sulfoxide," 15 J. Pharm. Pharma. Col. 688-692 (Oct. 1963).

Faust, "Some New Components for Cosmetic and Dermatologic Vehicles," 77 American Perfumer 23-26 (Jan. 1962).

Marson, "Il Dimetilsolfossido Solvente Aquo-Mimetico," 102 Boll. Chimicofarm. 109-124 (Feb. 1963).

Lubowe is a patent directed to compositions with large amounts of mineral, vegetable or animal oils solubilized in short chain alcohols. The oils are maintained in solution by the addition of fatty alcohols having 10 to 24 carbon atoms. The resulting compositions may be used as a base in a number of further cosmetic and pharmaceutical compositions. When the composition is used in a hair lotion, Lubowe indicates that "estrogenic hormones, methyl sulfoxide" may be added. Example XII shows a hair lotion containing 0.1% estrogenic hormone in 50% ethyl alcohol but without DMSO.

Brown et al. shows DMSO to be a solvent in which many classes of compounds are soluble and, further, is of low toxicity.

Faust suggests that DMSO is a "safe and effective solubilizing" agent suitable for use as a cosmetic or dermatologic vehicle.

Marson cites Faust saying "the cosmetic literature has recently cited its [DMSO's] employment as simple, non-gelated components of dermatological vehicles" and describes the usefulness of DMSO in preparing pharmaceutical compositions containing, inter alia, the thickening agents such as recited in the claims.

Background

The examiner indicated in the Final Rejection and in his Answer that the claims were rejected under 35 USC 103 since "the Lubowe patent describes, inter alia, DMSO added to Ex. XII, an anti-seborrheic hair lotion containing 1/10 part by weight of estrogenic hormone," and that, "we have, inherently, the same process involved here as described in Lubowe, notwithstanding applicant's observation of percutaneous absorption from the DMSO (apparently added as a vehicle or solvent, according to Faust, Marson or Brown)."

The board, in a first opinion, agreed with the Examiner's position and amplified it, stating:

> We note that the secondary references make it clear that DMSO is an effective solubilizing agent for various drugs, including those to be applied topically and along with the examiner we emphasize that ". . . an amount of DMSO sufficient to effectively enhance penetration . . ." of the steroid is also an amount effective for solubilization of the steroid; compare with page 19 of the specification. Therefore, we find that it would be obvious to add DMSO to the steroid containing formulation of Example XII of Lubowe in amounts large enough to enhance penetration of said steroid, in view of the teachings of the secondary references regarding DMSO's utility as a solvent for topical drug formulations.

The board made an additional rejection

> Under the provisions of 37 CFR 1.196(b) we make new grounds of rejection under 35 USC 102(b) and 35 USC 103 against claims 1 to 5 and 9 to 13.
>
> Claims 1 to 5 and 9 to 13 are rejected under 35 USC 102 and 35 USC 103 as unpatentable over any one of Stoughton et al, Stoughton or Kligman. All of the above publications were made of record by appellant's counsel in Paper No. 6 of great-grandparent case Serial No. 329,151 filed December 9, 1963. The above articles were described in detail by appellant's counsel in said Paper No. 6 (pages 8 to 12) and we will not, therefore, elaborate on the disclosure of the articles. It is sufficient to note that each of the articles teaches the enhanced penetration of various steroids resulting from topical application of DMSO concurrently with the steroid — the heart of appellant's inventive concept. All of the above articles were published in 1964 or 1965, more than one year prior to the filing date of appellant's grandparent case Serial No. 753,231, filed August 16, 1968. Hence the articles are statutory bars against the present claims under 35 USC 102(b) and 103 *unless* appellant's claimed invention was described in great-grandparent case Serial No. 329,151 filed December 9, 1963; see 35 USC 120 and 35 USC 112, first paragraph.
>
> We have carefully considered the great-grandparent case but the only disclosure relating to steroids (pages 34-35) is limited to glucocorticosteroids whereas *all* of the present claims on appeal are drawn either to steroids in general or to steroids not limited to glucocorticosteroids (claims 4-5). It is now well settled law that disclosure of a species is insufficient to provide descriptive support for a generic or sub-generic claim; In re Ruscetta et al, 45 CCPA 968, 255 F.2d

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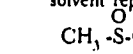
* The Honorable Shiro Kashiwa of the United States Court of Claims, sitting by designation.

** The Honorable Morgan Ford of the United States Customs Court, sitting by designation.

[1] This application is a division of serial No. 69,155, filed September 2, 1970, now U.S. 3,711,606, which in turn is a continuation-in-part of serial No. 753,231, filed August 16, 1968, now U.S. 3,551,554, which is a continuation-in-part of application serial No. 329,151 (hereafter the "great-grandparent"), filed December 9, 1963, now abandoned.

[2] Dimethyl sulfoxide (hereinafter DMSO) is a water-clear, water-miscible, hygroscopic, neutral organic liquid, melting at about 18°C. and boiling at about 189°C. It is a well-known industrial solvent represented by the following formula:



[3] 37 CFR 1.196(b) provides, in pertinent part, that:

> (b) Should the Board of Appeals have knowledge of any grounds not involved in the appeal for rejecting any appealed claim, it may include in its decision a statement to that effect with its reasons for so holding, which statement shall constitute a rejection of the claims.

[4] These references were not part of the certified record transmitted to the court. However, appellant admits in his brief that the rejection is proper *if* the great-grandparent lacks a written description of the invention in issue. The contents of the references need not be considered.

687, 118 USPQ 101 (1958), In re Lukach, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971) and In re Smith, 59 CCPA 1025, 458 F.2d 1389, 173 USPQ 679 (1972).

Hence, appellant may not rely upon his great-grandparent case to support any of the claims on appeal and thus the above articles are prior art and can be properly applied against the claims under 35 USC 102(b) and 103. We note also that the great-grandparent case was filed in the name of Jacob and Herschler, whereas the present case was filed by Herschler alone. Since the inventive entities are different, we do not see how appellant can claim priority under 35 USC 120 based upon the great-grandparent case; note the requirement that the applications be ". . . filed by the same inventor . . . ."

[Emphasis in original.]

Appellant thereupon submitted a Request for Reconsideration accompanied by two attachments and requested that the examiner consider them. The first attachment was a portion of a 508 page collection of papers given at a conference entitled Conference on Biological Actions of Dimethyl Sulfoxide held by the New York Academy of Sciences in 1974. The second enclosure was a copy of a Rule 45 declaration[1] submitted in the great-grandparent application purporting to amend the inventorship from Jacob and Herschler joint to Herschler sole.

In support of the Rule 45 affidavit, appellant argued:

> With respect to the first reason, submitted herewith are copies of papers filed under Rule 45 in the great-grandparent application, and a copy of a postcard receipt indicating that the papers were received by the Patent Office. The papers include an amendment under Rule 45 to change the inventorship of the great-grandparent application to correspond to the inventorship of this application. No notice was received that entry of the amendment was refused. Moreover, the Rule 45 papers were filed simultaneously with a continuing application in the name of the new inventorship and the Patent Office accorded continuation-in-part status to the application, which issued as U.S.P. 3,551,554. Hence, it is evident that the examiner considered the papers filed under Rule 45 and acknowledged that they were legally sufficient to change the inventorship. However, if the examiner believes it is necessary to formally change the inventorship of the great-grandparent application, he is invited to enter the Rule 45 amendment nunc pro tunc.

Appellant further argued that the written description in the great-grandparent was adequate for the subgenus now claimed:

> As clearly indicated in the great-grandparent application, appellant recognized from the start that the invention was applicable to physiologically active agents in general. * * * Thus, the Board's contention that "the only disclosure [in the great-grandparent application] relating to steroids is limited to glucocorticosteroids" is incorrect. The great-grandparent application discloses that the invention is applicable to the genus of physiologically active agents, which includes the important subgenus of steroids. A working example illustrates practice of the invention with a corticosteroid, which, of course, is a species of the subgenus of steroids. Hence, the great-grandparent application, in teaching the applicability of the invention to the genus of physiologically active agents in general, and to the species corticosteroids in particular, quite naturally describes to one skilled in the art the applicability of the invention to the subgenus of steroids. Since a corticosteroid is obviously a type of steroid, and since the word "corticosteroid" contains the very word "steroid", the corticosteroid in the working example, in view of the applicability of the invention to physiologically active agents in general, clearly represents to one skilled in the art the subgenus of steroids. There is no other subgenus that it would reasonably represent.

[1] Rule 45(b) of the Rules of Practice in Patent Cases provided, at the time of the affidavit in issue (1965), that:

> (b) If an application for patent has been made through error and without any deceptive intention by two or more persons as joint inventors when they were not in fact joint inventors, the application may be amended to remove the names of those not inventors upon filing a statement of the facts verified by all of the original applicants, and an oath or declaration as required by rule 65 by the applicant who is the actual inventor, provided the amendment is diligently made. Such amendment must have the written consent of any assignee.

The collection of papers submitted to the New York Academy of Sciences was said to demonstrate that "in view of the interest in DMSO generated by appellant's discovery, as shown by this reference, the discovery was truly a pioneering breakthrough in medical science." And further, that the papers describing work by:

> Kligman and others with just a few different species of steroids [show], that DMSO enhances the penetration of steroids in general. This same conclusion would similarly be drawn by one skilled in the art from the disclosure in appellant's great-grandparent application. Thus, the great-grandparent application describes to one skilled in the art the invention claimed in this application.

The board remanded the application to the examiner for consideration of the appended paper. In a supplemental Answer, the examiner stated:

> The Examiner respectfully declines the invitation to either now enter, nunc pro tunc, in an abandoned application, or to even consider what precisely Stanley Jacob did, or not, co-invent, in unverified copies of submitted purported Rule 45 amendment papers, which papers, even if not untimely, are unclear: ("various embodiments", "several additional embodiments", "I was informed on July 18, 1968 that I was not a coinventor", etc.), and considers them not relevant or sufficiently precise to any specific issues herein of whether or not he did not in fact co-invent the applicable portions of S.N.329,151, filed jointly with him, which relate to DMSO topically applied with a species of glucocorticosteroid * * *. [Furthermore, the board expressly states that] "we have carefully considered.", but they found, (and appellant has not denied,) that its only disclosure relating to steroids (pages 34-35) is limited to the single species of glucocorticosteroids, whereas *all* of the present claims on appeal are drawn either to steroids in general, or to steroids not limited to glucocorticosteroids (claims 4-5), and the Board of Appeal [sic] held it to be now well settled law that disclosure of a species is insufficient to provide descriptive support for a generic or sub-generic claim, citing the Ruscetta et al, Lukach and Smith decisions. Assuming, arguendo, that the precise inventorship of said glucocorticosteroid species and DMSO is established as not involving a different inventorship question; the question remains, for review under 35 USC 141 or 145, where, in S.N. 329,151, is described the steroid genus or subgenus, now claimed? [Emphasis in original.]

The application was then returned to the board. Appellant filed another request for reconsideration reiterating the comments and arguments made in the earlier request.

The board's final opinion indicated that:

> We agree with the Examiner that the unverified and unclear papers purportedly filed under 37 CFR 1.45 do not establish that the inventorship of 329,151 and that of the instant case are the same.
>
> We have carefully reconsidered our new ground of rejection under 35 USC 102(b) and 103 over the newly cited art but we are convinced that the rejection is sound. Apart from the different inventive entities of 329,151 and the instant case we remain of the view that there is no description [in] 329,151 of the process as applicable to steroids. In In re Smith, 178 USPQ 620 (1973), there was also a description in the parent case of a broad genus and a particular species, yet the CCPA held that there was insufficient descriptive support for a subgeneric claim similar to the present subgenus claims drawn to steroids. We do not see how an article published in 1974 or 1975 can aid appellant in overcoming the deficiencies in disclosure of an application filed December 9, 1963. The fact remains that nowhere in Serial No. 329,151 is there any mention of the term "steroids," let alone a description of the claimed process as applicable to steroids as a class.
>
> We reiterate our position that claims 1 to 5 and 9 to 13 are obvious over Lubowe in view of any one of Faust, Marson or Brown under 35 USC 103. We do not agree with appellant that it would not be obvious to solubilize steroids (such as the estrogenic hormone in Example XII of Lubowe) with DMSO. As explained by the Examiner in his answer, the secondary references make it clear that DMSO is an effective solubilizing agent for various drugs, including those to be applied topically. We emphasize again that ". . . an amount of DMSO sufficient to effectively enhance penetration . . ." of the steroid is also an amount effective for solubilization of the steroid. We therefore find clear motivation from the teachings of the prior art to solubilize steroids intended for topical application by adding DMSO to steroid formulations in an

amount sufficient to solubilize components of the steroid formulation. The fact that appellant may use DMSO for a different purpose (as compared to the prior art teachings that DMSO solubilizes drugs to be applied topically) does not alter the conclusion that its concomitant use with topically applied drugs such as estrogen would be prima facie obvious from the purpose disclosed in the references; In re Lintner, 173 USPQ 560, 562 (CCPA 1972).

Opinion

35 USC 102(b)/103 Rejection over Stroughton et al., Stroughton or Kligman

As noted above, appellant concedes that the substance of this rejection is proper if the court finds either the great-grandparent application lacks a written description of the instant invention[6] or the inventorship of the great-grandparent application differs from the one on appeal. The analysis need only consider those two points.

Rule 45 Affidavit

[1] The board found that the "unverified[7] and unclear papers * * * do not establish that the inventorship of 329,151 and that of the instant case are the same." We do not agree.

Jacob's affidavit indicated that he learned of the invention from the appellant:

> Herschler disclosed at this meeting his conception of the invention of enhancing tissue penetration of physiologically active agents by applying them to animal tissue (both topically and internally) together with DMSO and his reduction to practice of various embodiments of this invention. Herschler requested at this meeting that my group test various additional embodiments of this invention for him.

and that his participation "concerning the invention disclosed and claimed in application Serial No. 329,151 was limited to assisting in further testing of the invention with such additional pharmacologically active agents."

Although the affidavit is somewhat vague regarding specific acts done by the affiant, it is quite clear that he derived all information pertinent to the disclosed invention from Herschler and acted only under Herschler's direction. The affidavit is consistent with a finding that Jacob was not an inventor in the great-grandparent application. The accompanying affidavit of Herschler (ratifying the statement of Jacob), in conjunction with the originally filed application papers, leads us to the conclusion that Herschler believes himself to be the inventor of the matter disclosed and claimed in the great-grandparent application.

[2] This is not to say that we agree with appellant that the inventorship of the great-grandparent application was effectively amended by the PTO's acquiescence in accepting the sole inventorship of the grandparent nor do we agree that the great-grandparent was amended nunc pro tunc by the submission of copies of the Rule 45 papers. We consider the affidavits sufficient, for the purpose of claiming priority under §120, to demonstrate that Jacob was joined as a coinventor through error without deceptive intent. Weil v. Fritz, 572 F.2d 856, 196 USPQ 600 (CCPA 1978); In re Schmidt, 48 CCPA 1140, 293 F.2d 274, 130 USPQ 404 (1961).

Written Description in the Great-Grandparent

The appealed claims recite a subgenus, i.e., physiologically active steroidal agents, not found in haec verba in the great-grandparent application.

Appellant emphasizes the following quotation found in the great-grandparent specification and argues that it clearly defines a genus to which the subgenus of steroids belongs:

> By the term "physiologically active substance" is meant any substance which has a demonstrable and desired physiological activity in the sense that animal tissue responds thereto. This may be an altered physiologic phenomenon following heparin administration; a pharmacological activity such as local anesthesia; an antibacterial activity following administration of antibiotics; a bacteriostatic activity following the administration of iodine; a growth stimulation activity following usual access to dietary sources, and the like. The term is intended to include any desirable pharmacological action with compounds alien to animal tissue, and any physiological activity with compounds normally occurring in animal tissue. It is also meant to include within the term "physiologically active substance" materials which are diagnostic tools such as radiopaque agents (for instance, iodine), dyes and the like.

That application exemplifies a single species within the terms of claim 1 of this appeal:

> Example 30
>
> *Penetration of Corticosteroids*
>
> A twenty-four year old medical student was seen with atopic dermatitis of the right antecubital fossa. Three cc. of 100% dimethyl sulfoxide were applied four times daily for three days. No benefit was noted. One mg. or 1/4 cc. of Decadron (dexamethasone 21-phosphate) was applied four times a day for two days without benefit. One mg. of dexamethasone 21-phosphate in 3 cc. of 100% dimethyl sulfoxide was painted onto the involved area four times daily for three days. At the end of this period all evidence of the inflammatory reaction had disappeared.
>
> This example shows an improved action of dexamethasone 21-phosphate when used with dimethyl sulfoxide.

No other language in that specification specifically discusses topical application of a steroid-containing composition.

However, the remaining examples are awesome in their diversity. The scope of exemplified "physiologically active substances" includes iodine (Example 1), pressed pellet feed for rats (Example 4), penicillin (Example 10), procaine (Example 16), various chemotherapeutic agents (Examples 17 & 18), barbiturates (Example 19), oral insulin (Example 21), antihistamines (Example 29), various local anesthetics (Examples 34 & 35), etc.

[3] The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter later claimed by him; how the specification accomplishes this is not material. In re Smith, 481 F.2d 910, 178 USPQ 620 (CCPA 1973). The claimed subject matter need not be described in haec verba to satisfy the description requirement. In re Smith, 59 CCPA 1025, 458 F.2d 1389, 173 USPQ 679 (1972). It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations. In re Smythe, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

The question is simple: does the array of information supplied by appellant in the great-grandparent application teach one having ordinary skill in this art that one of the class of steroids will operate in the claimed process. We conclude that it does.

[4, 5, 6] A toehold on the problem is found in In re Cook, 58 CCPA 1049, 439 F.2d 730, 169 USPQ 298 (1971). The written description of a class of compounds must provide a measure of predictability for the utility described for that class. That is to say: would the worker of ordinary skill in this art consider "steroidal agents" to be operative when considering the great-grandparent's disclosure? It is incumbent, in the first instance, for the PTO to give reasons why he would not. In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 98 (CCPA 1976). The solicitor urges that the class of steroids is so large that a single example in the specification could not describe the varied members with their further varied properties. We disagree with this contention. Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids, when considered as a class of compounds carried through a layer of skin by DMSO, appear on this record to be chemically quite similar. The diversity of exemplified materials "potentiated" by DMSO in the great-grandparent application, is *much broader* than the diversity of steroid compounds shown contemporaneously in the art.[8] In this instance, we conclude that one having ordinary skill in this art would have found the use of the subgenus of steroids to be apparent in the written description of the great-grandparent application.

Were this application drawn to novel "steroidal agents," a different question would be posed.

[7] We wish to maintain the line first clearly drawn in In re Fuetterer, 50 CCPA 1453, 319 F.2d 259, 138 USPQ 217 (1963).

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[6] We assume, in the absence of any argument to the contrary, that the parent and grandparent applications contain the necessary written description of the invention on appeal. See In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

[7] It is not altogether clear what is meant by "unverified" in referring to the copy of the affidavit submitted to the examiner. The PTO had physical possession of the original affidavit at the time of the board decision as is evidenced by a certified copy thereof in the transcript submitted to the court. Further verification seems unnecessary.

[8] See, e.g., Kirk-Othmer, "Sterols and Steroids," 12 Encyclopedia of Chemical Technology 917-947 (1st Ed. 1954).

There, claims drawn to a rubber stock composition useful in producing tire treads included a recitation of "an inorganic salt capable" of maintaining an homogeneous distribution of another component in the composition. The disclosure listed the function desired and four members of the class having that function. This court found the written description requirement to be satisfied:

> Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.
>
> We are not persuaded that our conclusion on this point is wrong by decisions of this and other courts relating to the sufficiency of invention disclosures in cases wherein the applicant is claiming chemical *compounds* per se. [Emphasis in original.]

[8] Id. at 1462, 319 F.2d at 265-266, 138 USPQ at 223. Applications with claims either to intermediate classes of *new compounds* per se or claims drawn to processes *using* those *new compounds* have been considered by this court on other occasions. In re Driscoll, 562 F.2d 1245, 195 USPQ 434 (CCPA 1977); In re Ruschig, 54 CCPA 1551, 379 F.2d 990, 154 USPQ 118 (1967); In re Fried, 50 CCPA 954, 312 F.2d 930, 136 USPQ 429 (1963). The principles stated therein are still alive and well.

[9] In sum, claims drawn to the *use* of *known* chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description. In Fuetterer and here, such is the case.

35 USC 103 Rejection over Lubowe in view of Faust, Marson or Brown

Throughout the Lubowe patent, DMSO is mentioned only once, and that occurs in the statement that DMSO, as well as many other enumerated compounds, may be added to hair lotion preparations containing a solubilized oil. There is no indication of why the DMSO would be added; nor is there any teaching that there is any relationship between DMSO and estrogenic hormones (which are steroids), let alone a suggestion to employ them in combination. The board relies upon the secondary references to show "that DMSO is an effective solubilizing agent for various drugs, including those to be applied topically" and accordingly finds it obvious to utilize DMSO in Lubowe's Example XII. Such a conclusion is not supported by the record, because, as appellant notes, "the formulation of [Lubowe's] Example XII is already a clear solution containing more solvent than anything else. Moreover, the alcohol solvent employed in Lubowe is also a solvent for steroids." Hence, there would have been no reason for one skilled in the art to add any additional solvent to Lubowe's formulations, particularly a totally different solvent "in any amount large enough to enhance penetration," as required by the claims. Nor would it have been obvious to one skilled in the art to substitute DMSO for a portion of the exemplified alcohols, since Lubowe's invention is directed to the use of specific combinations of alcohols in the disclosed formulations.

While the secondary references may teach that DMSO is generally useful as a solvent, there is no suggestion or teaching in any of them to combine it with a steroid — that is, to choose DMSO from among the countless number of solvents as the solvent for steroids.

[10] Appellant argues that Brown, by stating that DMSO is "not known to interfere with absorption or metabolism," is a teaching not to use DMSO. The solicitor, on the other hand, characterizes the same quotation by saying that "it is not clear how this teaching is a teaching away * * * [and, accordingly] there should be no suprise [sic] that DMSO enhances penetration." Even though that quotation from Brown cannot be said to be an overwhelming suggestion to use DMSO for any solvent-type utility, we do not see how it provides any motivation for one skilled in the art to use DMSO in the formulation of Lubowe. The references do not provide any impetus to do what appellant has done nor do they provide the art with the knowledge that DMSO enhances penetration of "steroidal agents" through a membrane.*

Summary

We *reverse* the decision of the board, which decision affirmed a rejection of the claims both under 35 USC 102 and 103.

Reversed.

* We do not find it necessary to reach the question of the weight to be given the papers presented to the New York Academy of Sciences in that appellant has no prima facie showing of obviousness to rebut. Were such a showing appropriate, these papers could, if properly presented, indicate wide-scale acceptance in the art and provide a secondary consideration capable of overcoming a §103 rejection.

District Court, C. D. California

Bohsei Enterprises Company, U.S.A.
v. Porteous Fastener Company, et al.

No. CV 77-1241
Decided Nov. 16, 1977

TRADEMARKS

1. Fraud and misrepresentation (§67.37)

Court in Alfred Dunhill Ltd. v. Interstate Cigar Co., Inc., 183 USPQ 193, did not decide that omission was not cognizable under Lanham Act.

2. Fraud and misrepresentation (§67.37)

Law of false representation includes omission of material fact of origin that affirmatively says in context in which fasteners are sold "I am a product of the United States"; concern over materiality of such omission particularly in context of imported goods was expressed by Congress when it enacted 19 U.S.C. 1304 requiring imported articles to be "marked in a conspicuous place as legible, indelibly, and permanently as the nature of the article (or container) will permit in such manner as to indicate to an ultimate purchaser * * * the country of origin of the article"; to hold that omission of such material fact is not such false representation as to affect competition of sale to detriment of seller who complies with mandate of 19 U.S.C. 1304 requires utterly naive view of realities of market place; more importantly, it would promote disregard for provisions of 19 U.S.C. 1304; experience has taught courts that concept of private attorney general has been vigorous and needed method for protection of competition under antitrust law; to eschew the justice that experience has shown courts by a judicial narrowing of concept of fraud and deceit since it is embodied in Lanham Act would be pure legal folly and must be rejected.

Action by Bohsei Enterprises Company, U.S.A., against Porteous Fastener Co., Russell, Burdsall & Ward, Inc., Rockford Screw Products of California, Lamson & Sessions, Inc., and ITT Harper, Inc., for Lanham Act violations, and unfair competition. On defendants' motions to dismiss. Motions denied.

Ervin, Cohen & Jessup, Beverly Hills, Calif., for plaintiff.

Thorpe, Sullivan, Workman, Thorpe & O'Sullivan, Los Angeles, Calif., for Porteous Fastener Company.

Sullivan & Cromwell, New York, N.Y., and Lillick, McHose & Charles, Los Angeles, Calif., for Russell, Burdsall & Ward, Inc.

Glad, Tuttle & White, Los Angeles, Calif., for Rockford Screw Products of California.

Thorpe, Sullivan, Workman, Thorpe & O'Sullivan, Los Angeles, Calif., for Lamson & Sessions, Inc.

Powers & Tilson, Los Angeles, Calif., for ITT Harper, Inc.

Real, District Judge.

The defendants have variously moved for dismissal of the action brought by plaintiff. More specifically the motions are:

1. By defendant Rockford Screw Products of California (hereafter Rockford) — Motion for Judgment on the Pleadings.
2. By defendant Russell, Burdsall & Ward, Inc. (hereafter Russell) — Motion to Dismiss.
3. By defendant ITT Harper, Inc., (hereafter ITT) — Motion to Dismiss, Strike and for More Definite Statement.

Plaintiff Bohsei Enterprises Company, U.S.A. (hereafter Bohsei) is in the business

this court from awarding damages to plaintiff for defendant's infringement. Such finding of laches, however, does not bar the award of injunctive relief as made hereinafter. E.g., Menendez v. Holt, 128 U.S. 514, 523 (1888); Safeway Stores v. Dunnell, 172 F.2d 649, 656, 80 USPQ 115,120 (9th Cir. 1949); Reid, Murdoch & Co. v. H. P. Coffee Co., 48 F.2d 817, 820, 8 USPQ 420, 422-423 (8th Cir. 1931); Rolls-Royce Motors Ltd. v. A & A Fiberglass, Inc., 428 F.Supp. 689, 696, 193 USPQ 35, 43-44 (N.D. Ga. 1977); G. D. Searle & Company v. MDX Purity Pharmacies, Inc., 275 F.Supp. 524, 532-533, 157 USPQ 301, 306-307 (C.D. Cal. 1967); Gillette Company v. Ed Pinaud Inc., 178 F.Supp. 618, 622, 123 USPQ 531, 533-534 (S.D. N.Y. 1959).

[2] 10. The existence of third-party infringers does not preclude defendant's being enjoined from continuing the infringement of plaintiff's trademarks nor from continuing its unfair competition. See United States Jaycees v. San Francisco Jr. Cham. of Com., 354 F.Supp. 61, 67, 73, 175 USPQ 525, 529, 533-534 (N.D. Cal. 1972), affirmed, 513 F.2d 1226, 185 USPQ 257 (9th Cir. 1977); Rolls-Royce Motors Ltd. v. A & A Fiberglass, supra; 4 Callmann, Unfair Competition, Trademarks and Monopolies §87.3(e) at 152 (1969).

11. Defendant has committed acts of unfair competition by using plaintiff's trademarks in its catalogues and on its merchandise.

12. Plaintiff has not committed acts which violate the antitrust laws of the United States and defendant is not entitled to the relief sought in its counterclaim.

13. Plaintiff is entitled to equitable protection in the form of permanent injunctive relief from defendant's trademark infringement and unfair competition.

14. Said permanent injunctive relief shall be effective from and after January 1, 1978. Plaintiff is hereby directed to submit a form of permanent injunction consistent with the foregoing.

Court of Customs and Patent Appeals

In re Edwards, Rice, and Soulen

No. 77-532 Decided Jan. 12, 1978

PATENTS

1. Patentability — Anticipation — Patents — In general (§51.2211)

Patent, by same inventive entity, that was issued less than one year before parent application, whose filing date applicants are entitled to rely on, is removed as reference under 35 U.S.C. 102(b).

2. Patentability — Anticipation — Patents — In general (§51.2211)

Applicants who filed their parent application within one year of effective date of only reference are within one-year grace period allowed by 35 U.S.C. 102(b).

3. Specification — Sufficiency of disclosure (§62.7)

Function of description requirement is to ensure that inventor had possession of specific subject matter later claimed by him as of filing date of application relied on; it is not necessary that application describe claimed invention in ipsis verbis to comply with description requirement; all that is required is that it reasonably convey to persons skilled in art that inventor had possession of subject matter later claimed by him, as of its filing date; each case that inquires into whether parent application provides adequate direction that reasonably leads persons skilled in art to later claimed compound turns on its own specific facts, by its very nature.

4. Claims — Article defined by process of manufacture (§20.10)

Specification — Sufficiency of disclosure (§62.7)

Description of claimed compound that describes it by process of making it is not intrinsically defective; however, each case must be decided on its own facts; Court of Customs and Patent Appeals' primary concern in deciding whether application complies with written description requirement is not with mode selected for compliance; application that adequately describes process that will inherently produce compound does not necessarily adequately describe compound.

5. Claims — Broad or narrow — Markush type (§20.205)

Applicant claiming reactant as Markush group consisting of two members is asserting that these two members are alternatively usable for purposes of invention, and, therefore, resulting compound produced by overall process will exhibit disclosed utility regardless of which is chosen.

6. Pleading and practice in Patent Office — Rejections (§54.7)

Specification — Sufficiency of disclosure (§62.7)

Burden of showing that claimed invention is not described in application rests on Patent and Trademark Office that must give reasons why description not in ipsis verbis is insufficient and statement by Board of Appeals that Court of Customs and Patent Appeals has "significantly tightened up" on written description requirement in recent line of cases is no substitute for such reason; precedential value of prior case is extremely limited, since each case must be decided on its own facts.

Particular patents — Polyols

Edwards, Rice, and Soulen, Water Insoluble Nitrogen-Containing Polyols, rejection of claim 3 reversed.

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of Gayle D. Edwards, Doris M. Rice, and Robert L. Soulen, Serial No. 110,599, filed Jan. 28, 1971, continuation in part of application, Serial No. 682,560, filed Nov. 13, 1967, continuation in part of application, Serial No. 288,474, filed June 17, 1963. From decision rejecting claim 3, applicants appeal. Reversed; Miller, Judge, dissenting with opinion.

James L. Bailey, Houston, Tex., for appellants.

Joseph F. Nakamura (Fred W. Sherling, of counsel) for Commissioner of Patents and Trademarks.

Before Markey, Chief Judge, and Rich, Baldwin, Lane, and Miller, Associate Judges.

Lane, Judge.

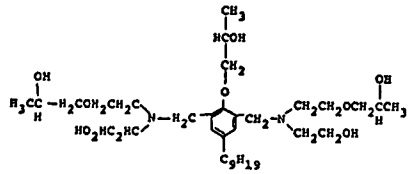
This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the final rejection of claim 3, the sole claim in application

serial No. 110,599, filed January 28, 1971, entitled "Water Insoluble Nitrogen-Containing Polyols."[1] We reverse.

The Invention

Appellants' invention is directed to a water-insoluble polyol (a poly-hydroxyl compound) which has sufficient self-catalytic activity to react, without the need of extraneous catalysts, with organic polyisocyanates to form rigid polyurethane foams. It is asserted that the foams produced from the polyols of the present invention are characterized by greater ease of fire retardancy and good dimensional strength when extraneous fire retardants are employed. Claim 3, the sole claim on appeal, reads as follows:

> 3. A water-insoluble polyol having the property of self-catalyzing reaction with organic polyisocyanates to form rigid polyurethane foam said polyol having the formula



As will become evident below, it is essential that the two reactions required to produce the claimed polyol be described. In the first reaction, which can generally be described as a Mannich reaction,[2] paranonylphenol,[3] diethanolamine, and formaldehyde are reacted in a molar ratio of 1:2:2; the predominant component of the resulting MRP will be a pentol (a compound with five hydroxyl groups). The second reaction, which appellants denominate as a propoxylation reaction, involves reacting propylene oxide with the MRP in a molar ratio of 3:1. The predominant product of this reaction will be the claimed compound, viz., a pentol with three degrees of propoxylation.[3]

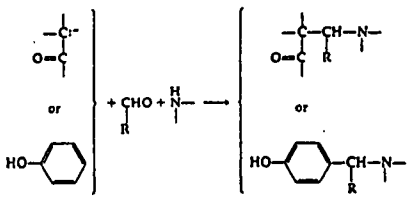
Prosecution History and the Rejection

The examiner finally rejected claim 3 on three separate grounds: (1) under 35 USC 112, second paragraph, as being indefinite; (2) under 35 USC 103, as being obvious over Bruson et al., U.S. Patent No. 2,998,452, issued August 29, 1961; and (3) under 35 USC 102(b), as being anticipated by Edwards et al., U.S. Patent No. 3,297,597, issued January 10, 1967, on an application filed May 23, 1966; the grandparent of this application is serial No. 288,474, filed June 17, 1963, which is the same application from which appellants' application originated (i.e., appellants' grandparent application). With respect to the §102(b) rejection, the examiner was of the opinion that neither the grandparent nor parent applications provided a written description (35 USC 112, first paragraph) of the claimed compound; consequently, appellants' claim that they were entitled to their earlier filing dates under 35 USC 120 was denied. By restricting appellants to their actual filing date (January 28, 1971), Edwards et al. (which issued January 10, 1967) constituted a statutory bar.

[1] The board reversed the first two grounds of rejection but affirmed the §102(b) rejection. Since the parent application was filed *less* than one year after the Edwards et al. patent issued, the board correctly concluded that if appellants were entitled to rely on its filing date, Edwards et al. (same inventive entity as appellants) would be removed as a reference under §102(b). In view of appellants' concession that Edwards et al. did, in fact, disclose the claimed

[1] The application is a continuation-in-part of parent application serial No. 682,560, filed November 13, 1967, which, in turn, is a continuation-in-part (the examiner had required it to be denominated as such and appellants, while referring to it below as a continuation, have, in their brief before us, referred to it as a continuation-in-part) of grandparent application serial No. 288,474, filed June 17, 1963.

[2] The Mannich reaction can be generalized as the linking of a carbanion site (enolate or phenolate) with an aldehyde and an amine. The following is the general reaction scheme:



Hereinafter, the product of this reaction will generally be referred to as the MRP (Mannich reaction product).

[3] The product will, in reality, be a mixture of polyols each having various degrees of propoxylation; the predominant component will, however, be the claimed polyol.

polyol, the sole remaining issue was whether the parent application provided a written description (35 USC 112, first paragraph) of the claimed polyol. Concluding that it did not, the board stated:

> [T]here is no description in said parent of the invention claimed in the present case. The only disclosure of nonyl phenol (required by claim 3 as the phenolic component) appears * * * with about twenty-five other phenols. While it might be obvious to combine . . . [this] disclosure * * * and Examples III or VIII, [that is to say] select *nonyl phenol* out of a list of twenty-five phenols, and then combine with propylene oxide in an amount sufficient to obtain the pentol of claim 3, we cannot agree that such selection and combination is equivalent to a "written description" of the claimed invention.
>
> We note that a recent line of CCPA cases have significantly tightened up on the application of the "written description" requirement of 35 USC 112, first paragraph; see In re Ruschig, 54 CCPA 1551, 379 F.2d 990, 154 USPQ 118 (1967); Fields et al v. Conover et al, 58 CCPA 1366, 443 F.2d 1386, 170 USPQ 276, 279-80 (1971) and In re Smith, 458 F.2d 1389, 173 USPQ 679, 683 (CCPA 1972). [Emphasis in original.]

Issue

The dispositive issue is whether appellants' parent application, serial No. 682,560, filed November 13, 1967, complies with the written description requirement of 35 USC 112, first paragraph, vis-a-vis the subject matter of the appealed claim; if it does, then the claim is entitled to the filing date of the parent application under 35 USC 120, In re Smith, 59 CCPA 1025, 458 F.2d 1389, 173 USPQ 679 (CCPA 1972), and Edwards et al. is removed as a reference.

Opinion

[2] While appellants argue that both the parent and grandparent applications provide an adequate written description of the claimed compound, in our view it is unnecessary to decide whether the grandparent application complies with the description requirement. Appellants filed their parent application within one year of the effective date (issue date) of the only reference - their own patent, and, as such, are within the one-year grace period allowed by §102(b). Cf. In re Gibbs, 58 CCPA 901, 437 F.2d 486, 168 USPQ 578 (1971).

Turning to the parent application, appellants assert that it, by virtue of providing an adequate written description of the aforementioned reactions, provides an adequate written description of the claimed polyol. That these reactions will produce, as the predominant product, the claimed polyol, is not in dispute. The board, however, took the position that the parent does not provide an adequate description of the two reactions; specifically, that it provides neither direction for selecting, as the phenolic reactant, para-nonylphenol, nor direction for choosing a propylene oxide/MRP molar ratio of 3:1.

[3] The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him. E.g., In re Blaser, 556 F.2d 534, 194 USPQ 122 (CCPA 1977); In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Smith & Hubin, 481 F.2d 910, 178 USPQ 620 (CCPA 1973). To comply with the description requirement it is not necessary that the application describe the claimed invention in ipsis verbis, In re Lukach, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971); all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him. See In re Driscoll, 562 F.2d 1245, 195 USPQ 434 (CCPA 1977). In the context of the present case, this translates into whether the parent application provides adequate direction which reasonably leads persons skilled in the art to the later claimed compound. See Flynn v. Eardley, 479 F.2d 1393, 17 USPQ 288 (CCPA 1973). By the very nature of this inquiry, each case turns on its own specific facts. See In re Driscoll, supra.

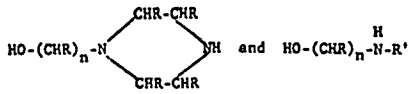
[4] As the board apparently recognized, the description in the parent is not intrinsically defective *merely* because appellants chose to describe their claimed compound by the process of making it; our primary concern is whether the description requirement has been complied with, not the mode selected for compliance. Cf. In re Smith & Hubin, 481 F.2d at 914, 178 USPQ at 624. It is undisputed that the aforementioned reactions will inherently produce, as the predominant component, the claimed compound. Further, the parent discloses that:

> Although it is within the scope of the present invention *to separate the crude * * * [MRP] by conventional means into specific components or fractions*, it is a feature of the pre-

sent invention that the entire crude Mannich reaction product may be used as such without attempting to isolate the individual components thereof. [Emphasis added.]

The parent application, therefore, recognizes that, if desired, conventional means can be used to separate components of the MRP and, ostensibly, of the final product. While it is true, as stated in the dissenting opinion, that in the preferred embodiment the parent does not separate the components, this does not negate the express disclosure that such separation is "within the scope" of the parent invention; if such express language does not evidence "possession," then nothing does. Thus, *on the facts of this case,* an adequate description of the aforementioned reactions is, concomitantly, an adequate description of the claimed compound. This should not be construed as meaning that if an application adequately describes a process which, inherently, will produce a compound, then it *necessarily* adequately describes the compound: Each case must be decided on its own facts.

[5] Example III, referred to by the board, discloses reacting phenol, diethanolamine, and formaldehyde in a molar ratio of 1:2:2; propylene oxide is then reacted with the resulting MRP in a molar ratio of 4.01:1. With respect to example III, we have noted that in their briefs, both appellants and the solicitor indicate that example III uses 3.6 moles of propylene oxide per mole of MRP; this is incorrect. Example III reacts 21.7 moles of propylene oxide with 5.41 moles of MRP, thus giving a molar ratio of 4.01:1. Original claim 2 of the parent application, which is part of the original disclosure, In re Gardner, 475 F.2d 1389, 177 USPQ 396, rehearing denied, 480 F.2d 879, 178 USPQ 149 (CCPA 1973), and to which the board made no reference, claims a polyol produced by reacting 1-7 moles of propylene oxide with one mole of the MRP of *phenol or nonylphenol,* an alkanolamine, and formaldehyde, reacted in a molar ratio of from 1:1:1 to about 1:3:3. The alkanolamine is selected from alkanolamines having the formulae:



where R is hydrogen or C_1-C_4 alkyl, R' is hydrogen, C_1-C_4 alkyl or -(CHR)n-OH, and n is a positive integer having a value of 2 to 5. Diethanolamine is a species which falls within these generic formulae. Moreover, of the eight working examples in the parent which describe making various polyols, *all eight* use diethanolamine as a reactant. This provides adequate direction for selecting diethanolamine as the alkanolamine in claim 2. Thus, claim 2 recites a process for producing a genus of compounds which includes both the predominant compound produced by example III and the claimed compound. More importantly, by claiming the phenolic reactant as a Markush group consisting of phenol or nonylphenol, it is generally understood that appellants are asserting that these two members are alternatively usable for the purposes of the invention, and therefore, regardless of which is chosen, the resulting compound produced by the overall process will exhibit the disclosed utility. See In re Driscoll, supra; see generally In re Skoll, 523 F.2d 1392, 1397, 187 USPQ 481, 484-85 (CCPA 1975). We view this as providing adequate direction for those skilled in the art to substitute nonylphenol for phenol in example III. The solicitor concedes as much in his brief; to conclude otherwise would make the statement in In re Lukach, 58 CCPA at 1235, 442 F.2d at 969, 169 USPQ at 796, that "the invention claimed does not have to be described *in ipsis verbis* in order to satisfy the description requirement of §112," meaningless.

Turning to the propylene oxide/MRP mole ratio in the second reaction, the solicitor's position is that, at best, the parent application describes the use of from 1 to 5 moles of propylene oxide per mole of MRP, and that "there is no specific teaching of * * * reducing the amount of propylene oxide to exactly 3 moles as required by the claimed compound." At oral argument, appellants asserted that while a propylene oxide/MRP molar ratio of 3 would, of course, produce the claimed compound, a somewhat larger ratio, such as the 3.6 used in example III, would also produce the claimed compound. As was previously shown, example III does not disclose the use of a molar ratio of 3.6. Moreover, in their brief before us, appellants stated that a molar ratio of 3 is required to produce the claimed compound. Therefore, for purposes of this appeal, we will assume that exactly 3 moles of propylene oxide per mole of MRP is required to produce the compound of appealed claim 3 (the board, in reversing the §103 rejection over Bruson et al., and the solicitor also stated that 3 moles is required).

To determine whether the parent application provides adequate direction for using the required propylene oxide/MRP molar ratio, an understanding of the underlying reactions is essential. Broadly stated, the parent application discloses first reacting a phenolic compound with an alkanolamine and formaldehyde, in molar ratios of from 1:1:1 to about 1:3:3, to produce an MRP. The resulting MRP potentially can contain three different types of reactive positions: phenolic hydroxyl group, free amino hydrogen atom, and primary hydroxyl group. In the second reaction, alkylene oxide (propylene oxide is disclosed as being preferred) will react with any of these three positions. The molar ratio used in the first reaction will determine whether the MRP is a triol, pentol, etc.; the molar ratio used in the second reaction will determine the degrees of propoxylation of the final product.

Applying this to example III, since the first reaction uses a molar ratio of 1:2:2 (phenol: diethanolamine: formaldehyde), the predominant MRP and the predominant final compound, like the claimed compound, will be a pentol; however, since example III uses a propylene oxide/MRP molar ratio of 4.01:1, the pentol will have four degrees of propoxylation, whereas the claimed pentol has three degrees of propoxylation. With respect to the degree of propoxylation, the parent application discloses that:

> In accordance with the present invention, the Mannich reaction product is reacted with an alkylene oxide to provide the final polyol. The nitrogen present in the Mannich condensate [MRP] has sufficient catalytic activity to promote the reaction of one mol of the alkylene oxide with each free amino hydrogen atom and phenolic and primary hydroxyl group and no additional catalyst is needed. * * * For example, seven mols [the stoichiometric amount] of propylene oxide will add to the Mannich product prepared from a molar ratio of 1:3:3 of phenol, diethanolamine and formaldehyde to give a heptol . . . .
>
> * * *
>
> *It is, of course, possible to add less than one mol of alkylene oxide per free phenolic and primary hydroxyl group in the Mannich condensation product. The minimum desirable amount of alkylene oxide is one mol per free amino hydrogen atom and phenolic hydroxyl group.* * * * *Generally, more than the minimum amount of alkylene oxide is used* to obtain a product having a lower hydorxyl [sic, hydroxyl] number and lower viscosity. For example, a desirable product is that obtained by the addition of five mols of propylene oxide *(rather than the maximum of seven or minimum of one)* to the heptol obtained by the Mannich condensation of phenol, formaldehyde and diethanolamine in a molar ratio of 1:3:3. [Emphasis added.]

The first reaction in example III, as well the first reaction required to produce the polyol of appealed claim 3, will produce, as the predominant MRP, a compound which has one phenolic hydroxyl group, no free amino hydrogen atoms, and four primary hydroxyl groups. With this in mind, we believe the above quoted disclosure would provide those skilled in the art with adequate direction for concluding that, in example III, from 1 (but preferably more than 1) to 5 moles of propylene oxide can be reacted with each mole of MRP and that, most importantly, the polyol produced *will have the disclosed utility;* ergo, it provides adequate direction for using three moles of propylene oxide in example III.

[6] When viewed in the context of what the parent application actually describes, the PTO has, in effect, done nothing more than argue lack of literal support. The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance, and it is to the PTO to give *reasons* why a descripti *not* in ipsis verbis is insufficient. In re Salem, 553 F.2d 676, 682, 193 USPQ 513, 518 (CCPA 1977); In re Wertheim, 541 F.2d at 265, 191 USPQ at 98. Stating, as the board did, that in a recent line of cases this court has "significantly tightened up" on the written description requirement, is no substitute for such reasons. Parenthetically, with respect to the board's perception of this court's past cases, suffice it to say that each case must be decided on its own facts, see, e.g., In re Driscoll, supra, and that precedential value of prior cases is, therefore, extremely limited.

In conclusion, we hold that, *as a factual matter,* the parent application, taken as a whole, reasonably leads persons skilled in the art to the reaction of para-nonylphenol, diethanolamine, and formaldehyde, in a molar ratio of 1:2:2, and to the reaction of propylene oxide with the resulting MRP, in

a molar ratio of 3:1, and, concomitantly, to the claimed compound. Accordingly, since claim 3 is therefore entitled to the benefit of the filing date of the parent application, we reverse the §102(b) rejection of this claim.

Reversed

Miller, Judge, dissenting.

As the majority opinion recognizes, the function of the description of the invention requirement of 35 USC 112, first paragraph, is to insure that an inventor had possession of the claimed subject matter as of the filing date of his application.

Appellants' parent application states that their invention involves "a new class of polyols"; also, it teaches use of the "entire crude Mannich reaction product" ("without attempting to isolate the individual components thereof") as the *preferred* embodiment of the invention in the further reaction with alkylene oxide to form polyol compounds within that class. From this disclosure, I am persuaded that one skilled in the art would conclude that appellants were not concerned with any specific polyol compound. Indeed, practice of the preferred embodiment of the invention would yield *mixtures* of polyol compounds.[1] (This does not ignore the statement in appellants' parent application that it is within the scope of the invention to separate the crude reaction product. However, merely being "within the scope of the invention" provides no guidance to convey clearly to one skilled in the art that appellants were in possession of the presently claimed subject matter; a preferred embodiment is a reliable guide, as the majority opinion acknowledges.)

I do not see how the majority can properly conclude that, "*on the facts of this case,* an adequate description of the * * * reactions [Mannich reaction and further reaction with alkylene oxide] is, concomitantly, an adequate description of the claimed compound," considering that the preferred embodiment in the parent application would yield an almost infinite number of different mixtures of polyol compounds. At best,[2] one of ordinary skill in the art, looking at the parent's claim 2 and example III on which the majority relies, would only be guided to a mixture of polyol compounds — not to the specific claimed polyol compound.[3] Nor can I accept the majority's conclusion that disclosure of from 1 to 5 moles "provides adequate direction [to one skilled in the art] for using three moles of propylene oxide in example III." There is nothing in appellants' parent application that would lead one to select 3 moles, rather than 1, 2, 4, 5, or the fractions thereof. The majority's assertion that "we will assume that exactly 3 moles of propylene oxide per mole of MRP is required to produce the compound of appealed claim 3" has no evidentiary support in the record.[4]

The majority opinion fails to explain why or how the mere disclosure of a mole range of a reactant that would result in the formation of an almost infinite number of different mixtures of polyol compounds, depending upon the number of moles of reactant chosen, provides an adequate description in this case, while the disclosure of at least 19 possible amine reactants in In re Ruschig, 54 CCPA 1551, 379 F.2d 990, 154 USPQ 118 (1967), and the naming of a number of possible substituents in Flynn v. Eardley, 479 F.2d 1393, 178 USPQ 288 (CCPA 1973), and Fields v. Conover, 58 CCPA 1366, 433 F.2d 1386, 170 USPQ 276 (1971), did not. Absent an explanation, the decision of the board should be affirmed.

[1] It should be noted that claim 1 (also dependent claim 2), for example, recites "polyol." However, the claims actually are to polyol compounds.

[2] Also noteworthy is the lack of direction (to one skilled in the art) of how to select the correct phenolic compound as an initial reactant. Appellants have admitted that some experimentation would be involved. Thus, although the enablement requirement of 35 USC 112 might be satisfied, the description of the invention requirement is not. In re DiLeone, 58 CCPA 925, 436 F.2d 1404, 168 USPQ 592 (1971).

[3] The majority improperly assumes that one skilled in the art would find appellants' parent application directed to individual polyol compounds and that, therefore, a disclosure of a range of from 1 to 5 moles of alkylene oxide reactant would result in the formation of only five compounds. This ignores the fact that the preferred embodiment of the parent application calls for the entire crude Mannich reaction product which, upon further reaction with alkylene oxide, would yield an almost infinite number of different mixtures of polyol compounds.

[4] Although the Solicitor appears to admit that reaction of 3 moles of propylene oxide with the appropriate Mannich reaction product will yield the claimed compound, neither the examiner nor the board did so, and no disclosure in appellants' parent application supports such a conclusion. The board referred to combining propylene oxide "in an amount sufficient to obtain the pentol of claim 3," and the examiner referred to a *product* containing a specific mole ratio.

District Court, S. D. New York

Mushroom Makers, Inc.
v. R. G. Barry Corporation

No. 76 Civil 1589 Decided Nov. 22, 1977

TRADEMARKS

1. Infringement — Tests of (§67.439)

UNFAIR COMPETITION

Unfair competition, trademarks and trade names compared (§68.95)

Touchstone of trademark infringement under Lanham Act is likelihood of confusion, that is, whether substantial number of ordinarily prudent purchasers are likely to be misled or confused as to source of different products; law of trademark infringement is part of law of unfair competition and same test is applied with respect to claims under each.

TRADEMARKS

2. Class of goods — How determined — In general (§67.2031)

Infringement — In general (§67.431)

Fact that products are not identical does not foreclose relief to senior owner if they are sufficiently related to make confusion likely; fact of seniority does not by itself entitle first user to relief; determination is made on basis of equities involved which requires evaluation of legitimate interests of senior user in being able to enter related field at some future time and protecting his mark from possibility of being tarnished by inferior merchandise of junior user, and of public in not being misled by confusingly similar marks.

3. Infringement — In general (§67.431)

Senior user has interest in preventing others from getting free ride on reputation and goodwill he has established, that is, from reaping harvest he has sown.

4. Infringement — Tests of (§67.439)

Factors that are to be evaluated in deciding whether trademark owner is entitled to relief against junior user of mark on noncompetitive item include, but are not limited to, strength of his mark, degree of similarity between two marks, proximity of products, likelihood that prior owner will "bridge gap," actual confusion, and reciprocal of junior user's good faith in adopting its own mark, quality of junior user's product, and sophistication of buyers.

5. Infringement — Tests of (§67.439)

Factors set out in Polaroid Corp. v. Polarad Electronics Corp., 128 USPQ 411, to consider in determining infringement in trademark cases dealing with noncompetitive products are variable and relative and no single one is determinative, but all pertinent factors must be considered and determination is made as to whether relief is warranted upon balancing of conclusions reached on pertinent factors.

6. Infringement — Tests of (§67.439)

It is not essential to protect trademark rights that alleged trademark owner prc that mark has become famous or popula name, so that its use on any product at once suggests to average consumer that alleged owner is its source or origin.

7. Identity and similarity — Words — Similar (§67.4117)

Marks and names subject to ownership — Descriptive — How determined (§67.5073)

Marks and names subject to ownership — Descriptive — Misdescriptive or not descriptive — Particular marks (§67.5078)

Marks and names subject to ownership — Secondary meaning (§67.523)

Mark whose use on products sold by parties is nondescriptive or suggestive of their wares is arbitrary and fanciful mark; "Mushroom" is not descriptive of shoes, sandals, slippers, or women's sportswear finding that mark is fanciful, nondescript mark obviates need to pass upon contentio.. that mark has achieved secondary meaning; doctrine of secondary meaning refers to protection afforded geographic or descriptive terms that producer has used to such extent as to lead general public to identify producer or product with mark; thus, establishment of secondary meaning permits user to protect otherwise unprotectable mark; mark, use of which has created secondary meaning in that consuming public now identifies mark with owner and its goods, is famous mark; "Mushroom" and "Mushrooms" are for all intents and purposes identical.

8. Evidence — In general (§67.331)

Marks and names subject to ownership — Descriptive — How determined (§67.5073)

attempt to divert sales from other competitors who manufactured a less identifiable product. [Fruehauf] deliberately fed upon the identification factors which were intentionally designed into the Cornhusker 800 trailer by [TESCO's] president. Wilfulness and bad faith are clearly shown by the evidence of this case.

his finding is supported by the facts. ruehauf, without knowledge of or inquiry ito the functional and nonfunctional spects of the exterior design of the ornhusker 800, copied exactly not only the perior functional qualities of the TESCO ailer but also the exterior physical haracteristics by which that good reputaon was known to the purchasing public. It t only sought and received the benefits of ESCO's goodwill, but, by coupling the tter's reputation with its own well-known me, set upon a source of conduct which, practical effect, would destroy the good putation of TESCO.[*] The award of only enty percent of Fruehauf's profits is clear- inadequate to ensure that similar conduct ill not reoccur in the future.

Moreover, given the bad faith conduct of uehauf and the potentially devastating fect that conduct had on its weaker comtitor, TESCO, we are hesitant to limit the ward on the basis of the fine-tuned results a post-infringement market survey. The cision to purchase a product, while usually justified by the objective criteria of performance, is often predetermined by the subctive factor of the product's good reputaon previously existent in the marketplace.

Accordingly, the judgment and order of e District Court is affirmed except as to e recovery of profits. As to that, the cause remanded for entry of judgment in that nount which will award TESCO all of uehauf's profits from sales of the trailers pied from the Cornhusker 800 and ide-ins taken as part of the purchase price the sale of those trailers in Nebraska, wa and Minnesota during the period of ingement.

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[*] The District Court found:

Considering the number of Cornhusker 800s which have been manufactured by [TESCO] since [TESCO] began its manufacturing operation up to the present time and the number of copies made and sold by [Fruehauf], it is probable that it no longer can be said that the consuming public identifies the distinctive design of the Cornhusker 800 with [TESCO].

Court of Customs and Patent Appeals

In re Wertheim, et al.

No. 75-536 Decided Aug. 26, 1976

PATENTS

1. Applications for patent — Continuing (§15.3)

Patentability — Anticipation — Carrying date back of references (§51.203)

Patentability — Anticipation — Patents — In general (§51.2211)

Specification — Sufficiency of disclosure (§62.7)

Claims are entitled to filing dates of parent application under 35 U.S.C. 120 and foreign application that was filed less than one year before parent application under 35 U.S.C. 119 if parent and foreign applications comply with 35 U.S.C. 112, first paragraph, including description requirement, as to claims' subject matter.

2. Foreign patents (§38.)

Patentability — Anticipation — Carrying date back of references (§51.203)

Specification — Sufficiency of disclosure (§62.7)

All 35 U.S.C. 119 requires is that foreign application describe and seek protection for broadly same invention as described in U.S. application claiming its benefit.

3. Court of Customs and Patent Appeals — Issues determined — In general (§28.201)

Court of Customs and Patent Appeals — Issues determined — Ex parte patent cases (§28.203)

Court of Customs and Patent Appeals, in interests of judicial economy, declines entreaty to determine whether decision's broad rule is still valid, since stated issue is dispositive regardless of decision's validity in its own factual setting; court need not separately decide sufficiency of parent U.S. application of applicants who must have benefit of their foreign application, which contains disclosure regarding limitations that is virtually identical to parent application's, to antedate reference patent.

4. Specification — Sufficiency of disclosure (§62.7)

Description requirement's function is to ensure that inventor possessed, as of filing date of application relied on, specific subject matter later claimed by him, but how

specification accomplishes this is not material; application need not describe claim limitations exactly, but only so clearly that persons of ordinary skill in art will recognize from disclosure that applicants invented processes including those limitations.

5. Amendments to patent application — In general (§13.1)

Specification — Sufficiency of disclosure (§62.7)

Primary consideration, in determining whether application describes claim limitations sufficiently clearly that persons of ordinary skill in art will recognize from disclosure that applicants invented processes including those limitations, is factual and depends on invention's nature and amount of knowledge imparted to those skilled in art by disclosure; broadly articulated rules are particularly inappropriate in this area; mere comparison of ranges is not enough, nor are mechanical rules substitute for analysis of each case on its facts to determine whether application conveys to those skilled in art information that applicants invented claims' subject matter; court must decide whether invention applicants seek to protect by their claims is part of invention they described as theirs in specification; fact that what applicants claim as patentable to them is less than what they describe as their invention is not conclusive if their specification also reasonably describes what they do claim; form would otherwise triumph over substance, substantially eliminating applicant's right to retreat to otherwise patentable species merely because he erroneously thought he was first with genus when he filed; patent law provides for amending claims as well as specification during prosecution, so that 35 U.S.C. 112, second paragraph, "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention" does not prohibit applicant from changing what he regards as invention, or subject matter on which he seeks patent protection, during application's pendency.

6. Patentability — Anticipation — Carrying date back of references (§51.203)

Pleading and practice in Patent Office — Rejections (§54.7)

Specification — Sufficiency of disclosure (§62.7)

As in cases involving section 112 enablement requirement, Patent and Trademark Office has initial burden of presenting evidence or reasons why persons skilled in art would not recognize in disclosure description of invention defined by claims; pointing to fact that claim reads on embodiments outside description's scope satisfies burden, so that applicants whose claim recites solids content range of "at least 35%" and whose foreign application described 25-60% range have burden of showing that 60% upper limit of solids content described is inherent in claim's limitation "at least 35%"; it is immaterial in ex parte prosecution whether same or similar claims were allowed to others.

7. Interference — Interference in fact (§41.40)

Specification — Claims as disclosure (§62.3)

Specification — Sufficiency of disclosure (§62.7)

Originally filed claim in appealed application is its own written description; disclosure of patent issued after applicants' foreign application is not evidence of what those skilled in art considered conventional at time foreign application was filed for Section 112 purposes; fact that claim's limitation is not material does not matter when limitation is copied; immateriality excuses only failure to copy patent claim's limitation.

8. Specification — Sufficiency of disclosure (§62.7)

There is important practical distinction between broad generic chemical compound inventions in which each compound within genus is separate embodiment of invention, and invention in which range of solids content is but one of several process parameters; broader range does not describe narrower range where broad described range pertains to different invention than narrower and subsumed claimed range.

9. Patentability — Anticipation — Carrying date back of reference (§51.203)

Pleading and practice in Patent Office — Rejections (§54.7)

Specification — Sufficiency of disclosure (§62.7)

Fact that applicants' foreign application describes invention as employing solids contents within 25-60% range along with specific embodiments of 36% and 50% warrants conclusion, in context of process for making freeze-dried instant coffee from concentrated coffee, that persons skilled in

art would consider claimed process employing 35-60% solids content range to be part of invention; Patent and Trademark Office's mere argument of lack of literal support is not enough; In re Lukach, 169 USPQ 795, statement that invention claimed does not have to be described in ipsis verbis in order to satisfy 35 U.S.C. 112 description requirement would be empty verbiage if lack of literal support alone were enough to support 35 U.S.C. 112 rejection; burden of showing that claimed invention is not described in specification rests on Patent and Trademark Office in first instance, and it is up to it to give reasons why description not in ipsis verbis is insufficient.

10. Amendments to patent application — New matter (§13.5)

Pleading and practice in Patent Office — Rejections (§54.7)

Specification — Sufficiency of disclosure (§62.7)

New matter rejection resting on Patent and Trademark Office's conclusion that application as filed did not describe limitation is tantamount to rejection on 35 U.S.C. 112, first paragraph, description requirement.

11. Patentability — Anticipation — In general (§51.201)

Patentability — Invention — In general (§51.501)

Pleading and practice in Patent Office — Rejections (§54.7)

Disclosure in prior art of any value within claimed range is anticipation of claimed range; fact that rejections are under 35 U.S.C. 103 rather than 102 requires considering whether applicants' invention and patent's disclosure are directed to different purposes and whether persons of ordinary skill in art would not look to reference patent's grandparent application for solution to problem addressed by applicants.

12. Patentability — Invention — In general (§51.501)

Applicants may not use rationale, that patent and its grandparent application gave no hint of inventive concept of regulating product bulk density to show unobviousness without antecedent basis for it in their application.

13. Patentability — Invention — Specific cases — In general (§51.5091)

It would be obvious to reduce size of coffee foam particles by suitable mechanical process for making freeze-dried instant coffee, before, rather than after drying.

14. Patentability — Invention — In general (§51.501)

Applicants whose claim requires freezing over 7 to 25 minute period and who indicate that this produces coffee "having pleasant dark colour" have not overcome prima facie case of obviousness made out by reference disclosing instantaneous freezing, absent showing that only their claimed freezing time produces coffee of pleasant dark color.

15. Patentability — Invention — In general (§51.501)

Pleading and practice in Patent Office — Rejections (§54.7)

Specification — Sufficiency of disclosure (§62.7)

Fact that persons skilled in art may not know how to ensure claimed final product densities from specification is pertinent only to rejection on 35 U.S.C. 112, first paragraph, enablement requirement, and not to whether limitation distinguishes prior art under Section 103.

16. Patentability — Anticipation — Patent application (§51.219)

Specification — In general (§62.1)

Applicants' disclosure may not be used against them as prior art absent admission that matter disclosed in specification is in prior art.

17. Claims — Article defined by process of manufacture (§20.15)

Patentability — Invention — In general (§51.501)

Court of Customs and Patent Appeals does not subscribe to broad proposition that process limitations can never serve to distinguish apparatus claims' subject matter from prior art.

18. Patentability — Anticipation — Patents — In general (§51.2211)

Prior art patents are to be viewed for what they disclose in their entireties and not merely for their inventive contributions to art.

19. Claims — Article defined by process of manufacture (§20.15)

Patentability — Invention — In general (§51.501)

Pleading and practice in Patent Office — Rejections (§54.7)

Patentability of products defined by

processes for making them, is what must be gauged in light of prior art; fact that some products covered by applicants' product-by-process claims may not be suggested by reference patent's grandparent application that completely discloses other subject matter embraced by applicants' claims is not relevant to patentability, complete disclosure in prior art being epitome of obviousness; fact that applicants do not contend that they could not understand basis for rejection because of Patent and Trademark Office's failure to give clear reasons for its action under 35 U.S.C. 132 and explanations given by examiner and Board of Appeals were legally ample under section warrants conclusion that claims that were allegedly improperly grouped with other claims were subject of proper rejection.

Particular patents — Drying Method

Wertheim and Mishkin, Drying Method, rejection of claims 1, 4, 6-16, 21-28, 30-35, and 40-43 affirmed; rejection of claims 2, 17-20, 29, 37, and 38 reversed; appeal dismissed as to claims 3, 5, 36, and 39.

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of John H. Wertheim and Abraham R. Mishkin, Serial No. 96,285, filed Dec. 8, 1970, continuation of application, Serial No. 537,679, filed Mar. 28, 1966, claiming benefit of Swiss application filed Apr. 2, 1965. From decision rejecting claims 1, 2, 4, 6-35, 37, 38, and 40-43, applicants appeal. Modified; Baldwin and Miller, Judges, dissenting in part with opinions.

William H. Vogt III, and Watson Leavenworth Kelton & Taggart, both of New York, N.Y. (Paul E. O'Donnell, Jr., New York, N.Y., of counsel) for appellants.

Joseph F. Nakamura (Gerald H. Bjorge, of counsel) for Commissioner of Patents and Trademarks.

Before Markey, Chief Judge, and Rich, Baldwin, Lane, and Miller, Associate Judges.

Rich, Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals affirming the final rejection of claims 1-43, all the claims in application serial No. 96,285, filed December 8, 1970, entitled "Drying Method."[1] The appeal on claims 3, 5, 36, and 39 has been withdrawn, and as to these claims it is, therefore, dismissed. As to the remaining claims, we affirm in part and reverse in part.

The Invention

Appellants' invention centers around a process for making freeze-dried instant coffee. Claims 1, 6, 30, and 40 are illustrative:

> 1. An improved process for minimising loss of volatiles during freeze-drying coffee extract which comprises obtaining coffee extract, concentrating said extract to a higher solids level of at least 35%, foaming said concentrated extract to a substantial overrun by injection of a gas into said extract at at least atmospheric pressure to thereby avoid evaporative cooling due to evaporation of water in said extract during said foaming, freezing said foam to below its eutectic point at at least atmospheric pressure while avoiding evaporative cooling, and freeze-drying said extract at below the eutectic temperature of said extract.
>
> 6. Process for preparing a powdered coffee extract, which comprises adding sufficient inert gas to a concentrated aqueous extract of roast coffee containing about 25% to 60% by weight of soluble coffee solids to provide a foam having a density between about 0.4 and 0.8 gm/cc, freezing the foamed extract to a solid mass, grinding the frozen foam to a particle size of at least 0.25 mm and freeze drying the ground frozen foam.
>
> 30. An apparatus for carrying out the process defined in claim 6 comprising, in combination, means for foaming, a closed chamber capable of being maintained at a temperature which is substantially below the melting temperature of said frozen foam, and, disposed within said chamber, a movable endless belt, means for moving said belt at a low speed, a spreading device for distributing coffee extract foam on said belt and refrigerating means for cooling at least one surface of said belt with a liquid refrigerant.

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[1] A continuation (or continuation-in-part, as the examiner has required it to be denominated) of application serial No. 537,679, filed March 28, 1966. Appellants claim the benefit of a Swiss application filed April 2, 1965. The title of the application on appeal is somewhat inaccurate, as the application contains claims to apparatus for drying and dried instant coffee products as well as to a drying method.

40. A dry coffee powder comprising a freeze-dried particulated foamed extract of roast and ground coffee, the foam before freeze drying having a density between about 0.4 and 0.8 gm/cc.

The remaining claims are reproduced in the Appendix hereto. Appellants assert that their invention produces an instant coffee having a bulk density of 0.2-0.3 gm/cc, which corresponds to that of conventional spray-dried instant coffee.[2] They allege they discovered that this desired bulk density results from controlling the solids content of the concentrated extract prior to foaming and the density of the foam generated therefrom within the range of their freeze-drying process claims.

Since the claims are somewhat elliptical in setting out the steps of appellants' process, we shall describe it further. An aqueous extract of coffee is prepared by percolating hot water through roasted and ground coffee beans. The extract is concentrated to have a solids content between 25% and 60% and is then charged with gas to produce a foam having a density between 0.4 and 0.8 gm/cc. The foam is frozen and ground into particles, preferably 0.25 to 2.0 mm in size, which are freeze-dried by conventional techniques.

Prosecution History and Rejections

The claims which remain on appeal fall into two broad groups: The "interference" claims, 1, 2, 4, 37, and 38; and the "non-interference" claims, 6-35 and 40-43.

As originally filed, the application contained claims 1-5 copied from Pfluger et al. U. S. Patent No. 3,482,990 (Pfluger patent), issued December 9, 1969, on an application filed February 10, 1969. A letter under Rule 205(a), 37 CFR 1.205(a), requesting an interference with the Pfluger patent accompanied the application. By amendment, appellants transferred claims 6-35 from their 1966 application to the instant application. Claims 36-39, added by amendment, are modified versions of the previously copied claims and were presented for the purpose of providing a basis for phantom counts in an interference with the Pfluger patent under Rule 205(a) and Manual of Patent Examining Procedure §1101.02. They depend from claim 2.

[2] So that consumers may continue to use the same amount of freeze-dried instant coffee per cup as conventional instant coffee without change in the strength of the beverage that they are accustomed to.

The patents relied on by the examiner are:

Pfluger et al.	**3,482,990**	**Dec. 9, 1969**
De George	**3,253,420**	**May 31, 1966 (application filed Feb. 3, 1965)**
Carpenter et al.	**2,974,497**	**Mar. 14, 1961**
British patent	**948,517**	**Feb. 5, 1964**

The Pfluger patent issued on a chain of four applications: serial No. 800,353, filed Feb. 10, 1969, which was a continuation of serial No. 520,347, filed Jan. 13, 1966 (Pfluger 1966), which was a continuation-in-part of serial No. 309,410, filed Sept. 17, 1963 (Pfluger 1963), which was a continuation-in-part of serial No. 98,007, filed Mar. 24, 1961. The Pfluger patent discloses a process for making freeze-dried instant coffee which has as its goal minimizing the loss from a foamed extract of volatile aromatics which contribute substantially to the natural flavor of coffee and other foods.

De George describes apparatus and methods for freezing liquid, unfoamed coffee extract prior to drying on continuous belts refrigerated by brine tanks contacting the bottom surfaces of the belts. The claims of De George are directed to processes for facilitating the removal of the frozen sheet of coffee extract from the belt before it is freeze dried.

The British patent discloses a rapid freeze-drying process in which the food product is frozen, milled into small particles which are spread from a hopper in single-particle layers onto plates, and freeze-dried in a vacuum chamber. More details of the disclosure are supplied infra.

Carpenter discloses the cooling of a refrigeration belt by spraying cold brine onto the underside of the belt.

The examiner made multiple rejections which were addressed by the board in eight categories, seven of which are before us for review. Category I covers the "interference" claims, which were rejected on the Pfluger patent, claims 1, 2, and 4 under 35 USC 102 and claims 37 and 38 under §103. The board agreed with the examiner's position that these claims were not entitled to the benefit of appellants' 1965 Swiss priority date because they were not supported by appellants' parent and Swiss applications. The limitations held to be unsupported were "at least 35% [solids content]" in claim 1, "between 35% and 60% soluble solids" in claims 2 and 4, and "pressure of less than 500 microns" and "final product temperature of less than 110°F." in claim 4. For that reason appellants were held to be junior to the Pfluger patent on the basis of Pfluger's 1966 filing date. In light of appellants' refusal to file a Rule 204(c)[3] affidavit showing a date of invention prior to Pfluger's 1966 filing date, the examiner and the board held the Pfluger patent to be prior art under §102(e) against claims 1, 2, 4, 37, and 38 and rejected the claims on that basis.[4] The board refused to hold that the claims were supported in the parent and Swiss applications, "for interference purposes," under our decision in In re Waymouth, 486 F.2d 1058, 179 USPQ 627 (CCPA 1973), mod. on reh., 489 F.2d 1297, 180 USPQ 453 (CCPA 1974). The board stated that appellants' failure to file a Rule 204(c) affidavit precluded any attempt to get into an interference and that Waymouth, which concerned the right to make a claim for interference purposes in the application on appeal, was therefore inapplicable to this case.

Under Category II, the board affirmed the rejection of claims 6-10, 12-15, 17, and 26 under 35 USC 132 for new matter. The board held that these claims, which were added to the instant application by amendment, were not supported in the original disclosure for lack of a description of the claimed size of the ground foam particles, i.e., "at least 0.25 mm."

The Category III rejection was reversed by the board.

In Category IV, claims 6-8, 11-20, and 40-43 were rejected under §103 on the disclosure of Pfluger 1963[5] carried forward to the Pfluger patent, in accordance with In re Lund, supra. The board found that the foam density range of 0.4-0.8 gm/cc claimed by appellants (and the 0.6-0.8 gm/cc range in claims 19 and 20) was suggested by Pfluger 1963's disclosure of 0.1-0.5 gm/cc foam density and that Pfluger 1963 teaches the use of foaming gases and concentrating the coffee extract prior to foaming. The board found that the final product densities claimed would be inherent "in view of the same foam overrun density disclosed by Pfluger" and that Pfluger's example I, which discloses breaking the frozen foam strands into 3/4" lengths (i.e., "at least 0.25 mm") before drying, would suggest the size of the ground foam particles claimed by appellants.

Category V added De George to the §103 rejection of claims 9, 10, 30, and 32-35. The board agreed with the examiner that the temperatures, foam thicknesses, and belt lengths and speeds covered by these claims are disclosed in De George, and that it would be obvious to use De George's moving belt apparatus in the Pfluger process.

In Category VI claims 21-23 and 26-29 were rejected under §103 on Pfluger in view of the British patent, which was relied on for its teaching of the concentration of coffee extract by freezing to a solids content of 27 to 28%. Pfluger was applied to the claims under the rationale employed in Category IV.

Category VII was the rejection of claims 24 and 25 under §103 on Pfluger, the British patent, and De George, which was relied on to show "the deposition of a coffee extract on a moving belt prior to grinding and freeze drying." The board otherwise relied on the reasoning in Categories V and VI.

Under Category VIII claim 31 was rejected on Pfluger and De George under §103 for the reasons of Category V, with reliance on Carpenter to show refrigeration of the belt by spraying refrigerant onto the bottom of the belt instead of using De George's brine tanks.

[3] 37 CFR 1.204(c):

When the effective filing date of an applicant is more than three months subsequent to the effective filing date of the patentee, the applicant, before the interference will be declared, shall file two copies of affidavits or declarations by himself, if possible, and by one or more corroborating witnesses, supported by documentary evidence if available, each setting out a factual description of acts and circumstances performed or observed by the affiant, which collectively would prima facie entitle him to an award of priority with respect to the effective filing date of the patent. This showing must be accompanied by an explanation of the basis on which he believes that the facts set forth would overcome the effective filing date of the patent.

[4] The examiner and the board did not rely on Pfluger 1963 because the solids content and foam density ranges of the copied claims were not described in that application. In re Lund, 54 CCPA 1361, 376 F.2d 982, 153 USPQ 625 (1967).

[5] Peebles U. S. patent No. 2,897,084, issued July 28, 1959, was cited against claims 19 and 20 to show that agglomerating fine dried coffee particles into larger grounds was old in the art. Appellants have acknowledged this to be true, so it is not necessary to discuss Peebles further.

Opinion

The "Interference" Claims — 1, 2, 4, 37, and 38

[1] The dispositive issue under this heading is whether appellants' parent and Swiss applications comply with 35 USC 112, first paragraph, including the description requirement, as to the subject matter of

these claims. If they do, these claims are entitled to the filing dates of the parent application under 35 USC 120, In re Lukach, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971), and the Swiss application under 35 USC 119, Kawai v. Metlesics, 480 F.2d 880, 887-88, 178 USPQ 158, 164 (CCPA 1973). Since the PTO relies only on Pfluger 1966 to provide the effective U.S. filing date of the patent as a reference against these claims under §§102(e) and 103, a right of foreign priority in appellants' Swiss application will antedate Pfluger 1966 and remove it as prior art against the claims.

[2] The only defect asserted below in appellants' parent and Swiss application disclosures that covers all these claims is that the applications do not contain written descriptions of the solids content limitations of the concentrated extract prior to foaming, i.e., "at least 35%" (claim 1) and "between 35% and 60%" (claims 2, 4, 37, and 38).*

[3] Appellants' parent and Swiss applications contain virtually identical disclosures on this point. Both disclose that the coffee extract initially produced by percolation of water through ground roasted coffee is concentrated prior to foaming by suitable means "until a concentration of 25 to 60% solid matter is reached." Examples in each disclose specific embodiments having solids contents of 36% and 50%.

In our view, it is necessary to decide only whether the Swiss application complies with the description requirement of §112 with respect to the questioned limitations. There is no question that the *instant* application supports claims 1, 2, and 4, which are original claims in that application. Appellants and the solicitor urge us to decide this case by determining whether the broad rule of In re Waymouth, supra, is still valid or must be disapproved. In the interest of judicial economy, we decline this entreaty since the issue of whether the Swiss application contains written descriptions of the disputed limitations of claims 1, 2, 4, 37, and 38, being addressed to strict compliance with §112, first paragraph, is dispositive regardless of the validity of Waymouth in its own factual setting. The sufficiency of the parent U. S. application need not be separately decided since appellants must have the benefit of their Swiss application date to antedate the Pfluger patent.

[4] The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material. In re Smith, 481 F.2d 910, 178 USPQ 620 (CCPA 1973), and cases cited therein. It is not necessary that the application describe the claim limitations exactly, In re Lukach, supra, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations. In re Smythe, 480 F.2d 1376, 1382, 178 USPQ 279, 284 (CCPA 1973).

[5] The primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. The factual nature of the inquiry was emphasized in In re Ruschig, 54 CCPA 1551, 1558-59, 379 F.2d 990, 995-96, 154 USPQ 118, 123 (1967), which involved the question whether a broad generic disclosure "described" the single chemical compound claimed:

> But looking at the problem, as we must, from the standpoint of one with no foreknowledge of the specific compound, it is our considered opinion that the board was correct in saying:
>
> > Not having been specifically named or mentioned in any manner, one is left to selection from the myriads of possibilities encompassed by the broad disclosure, with no guide indicating or directing that this particular selection should be made rather than any of the many others which could also be made.
>
> Appellants refer to 35 USC 112 as the presumed basis for this rejection and emphasize language therein about *enabling* one skilled in the art to *make* the invention, arguing therefrom that one skilled in the art would be enabled by the specification to make chlorpropamide. We find the argument unpersuasive for two reasons. First, it presumes some motivation for

* The solicitor belatedly asserts that the Swiss application is not "for the same invention" as the parent application, insofar as claims 1, 2, and 4 are concerned; he argues that the expression "same invention" in 35 USC 119 should be given the meaning employed by us in the double patenting cases, e.g., In re Vogel, 57 CCPA 920, 422 F.2d 438, 164 USPQ 619 (1970). As we indicated in In re Ziegler, 52 CCPA 1473, 347 F.2d 642, 146 USPQ 76 (1965), the solicitor's reading is too narrow. All §119 requires is that the foreign application describe and seek protection for "broadly the same invention" as described in the U.S. application claiming its benefit. 52 CCPA at 1481, 347 F.2d at 649, 146 USPQ at 82. The Swiss application has essentially the same disclosure as appellants' parent application and claims broadly the same invention.

> wanting to make the compound in preference to others. While we have no doubt a person so motivated would be enabled by the specification to make it, this is beside the point for the question is not whether he would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. We think it does not. Second, we doubt that the rejection is truly based on section 112, at least on the parts relied on by appellants. If based on section 112, it is on the requirement thereof that "The specification shall contain a written description *of the invention* * * *." [Emphasis ours.] We have a specification which describes appellants' invention. The issue here is in no wise a question of its compliance with section 112, it is a question of *fact: Is the compound of claim 13 described therein?* Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound?

Broadly articulated rules are particularly inappropriate in this area. See, e.g., In re Smith, 59 CCPA 1025, 1033, 458 F.2d 1389, 1394, 173 USPQ 679, 683 (1972), in which this court felt obliged to overrule a supposed "rule" of In re Risse, 54 CCPA 1495, 1500-01, 378 F.2d 948, 952-53, 154 USPQ 1, 5 (1967). Mere comparison of ranges is not enough, nor are mechanical rules a substitute for an analysis of each case on its facts to determine whether an application conveys to those skilled in the art the information that the applicant invented the subject matter of the claims. In other words, we must decide whether the invention appellants seek to protect by their claims is part of the invention that appellants have described *as theirs* in the specification. That what appellants claim as patentable to them is *less* than what they describe as their invention is not conclusive if their specification also reasonably describes that which they do claim. Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable. As we said in a different context in In re Saunders, 58 CCPA 1316, 1327, 444 F.2d 599, 607, 170 USPQ 213, 220 (1971):

> To rule otherwise would let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed. Cf. In re Ruff, 45 CCPA 1037, 1049, 256 F.2d 590, 597, 118 USPQ 340, 347 (1958). Since the patent law provides for the amendment during prosecution of *claims*, as well as the specification supporting claims, 35 USC 132, it is clear that the reference to "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention" in the second paragraph of 35 USC 112 does not prohibit the applicant from changing what he "regards as his invention" (i.e., the subject matter on which he seeks patent protection) during the pendency of his application. Cf. In re Brower, 58 CCPA 724, [728] 433 F.2d 813, 817, 167 USPQ 684, 687 (1970) (fact that claims in continuation application were directed to subject matter which appellants had not regarded as part of their invention when the parent application was filed held not to prevent the continuation application from receiving benefit of parent's date).

[6] Claims 1 and 4 present little difficulty. Claim 1 recites a solids content range of "at least 35%," which reads literally on embodiments employing solids contents outside the 25-60% range described in the Swiss application. As in cases involving the enablement requirement of §112, e.g., In re Armbruster, 512 F.2d 676, 185 USPQ 152 (CCPA 1975), we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. By pointing to the fact that claim 1 reads on embodiments outside the scope of the description, the PTO has satisfied its burden. Appellants thus have the burden of showing that the upper limit of solids content described, i.e., 60%, is inherent in "at least 35%," as that limitation appears in claim 1. Appellants have adduced no evidence to carry this burden as to claim 1, and they argue only that since the Pfluger patent contains claim 1 supported by Pfluger's disclosure with a stated upper limit of 60%, like appellants' Swiss disclosure, refusal to grant appellants claim 1 amounts to an illegal reexamination of claim 1 in Pfluger. However, as we have often repeated, as recently as In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976), it is immaterial in ex parte prosecution whether the same or similar claims have been allowed to others.

[7] Claim 4 contains the additional limitations, relating to the "final product temperature" and the pressure at which the frozen foam is vacuum freeze-dried, of "less

than 110°F." and "less than 500 microns." "Final product temperature," it appears, refers to the temperature at which so-called bound water is driven off from the product by heating after the vacuum drying phase has ended. We find no description of final product temperature in appellants' Swiss application. It is not disputed that appellants do not expressly disclose final product temperatures or this secondary drying step. They again appeal, however, to the Pfluger patent disclosure and to an amendment entered in the application on appeal (not objected to as new matter by the examiner) to show that final product temperatures are conventional in the art and need not be expressly disclosed. The amendment is clearly irrelevant since claim 4, an originally filed claim, is its own written description in the appealed application. In re Gardner, 475 F.2d 1389, 177 USPQ 396, rehearing denied, 480 F.2d 879, 178 USPQ 149 (CCPA 1973). The issue is whether the Swiss application describes the claimed final product temperature, not whether the instant application does so. The Pfluger patent disclosure is also unavailable to appellants. The Swiss application was filed before Pfluger issued, which means that for the purposes of §112 the Pfluger disclosure is not evidence of what those skilled in the art considered conventional at the time the Swiss application was filed. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974).'

Claims 1 and 4, therefore, are not entitled to the benefit of the filing date of appellants' Swiss application.

[8] Claims 2, 37, and 38, which claim a solids content range of "between 35% and 60%," present a different question. They clearly claim a range *within* the described broad range of 25% to 60% solids; the question is whether, *on the facts*, the PTO has presented sufficient reason to doubt that the broader described range also describes the somewhat narrower claimed range. We note that there is no evidence, and the PTO does not contend otherwise, that there is in fact any distinction, in terms of the operability of appellants' process or of the achieving of any desired result, between the claimed lower limit of solids content and that disclosed in the Swiss application. We see an important practical distinction between broad generic *chemical compound* inventions, for example, as in In re Ruschig, supra, in which each compound within the genus is a separate embodiment of the invention, and inventions like that at bar, in which the range of solids content is but one of several process parameters. What those skilled in the art would expect from using 34% solids content in the concentrated extract prior to foaming instead of 35% is a different matter from what those skilled in the art would expect from the next adjacent homolog of a compound whose properties are disclosed in the specification. We wish to make it clear that we are not creating a rule applicable to all description requirement cases involving ranges. Where it is clear, for instance, that the broad described range pertains to a different invention than the narrower (and subsumed) claimed range, then the broader range does not describe the narrower range. In re Baird, 52 CCPA 1747, 348 F.2d 974, 146 USPQ 579 (1965); In re Draeger, 32 CCPA 1217, 150 F.2d 572, 66 USPQ 247 (1945).

[9] In the context of *this* invention, in light of the description of the invention as employing solids contents within the range of 25-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the Swiss disclosure so to conclude. Cf. In re Ruschig, supra. The PTO has done nothing more than to argue lack of literal support, which is not enough. If lack of literal support alone were enough to support a rejection under §112, then the statement of In re Lukach, supra, 58 CCPA at 1235, 442 F.2d at 969, 169 USPQ at 796, that "the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of §112," is empty verbiage. The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in ipsis verbis is insufficient.

We conclude, therefore, that claims 2, 37, and 38 are entitled to the benefit of the filing date of appellants' Swiss application.

Since the Pfluger patent is not available as prior art as of its 1966 date under §§102(e) and 103 against claims 2, 37, and 38, the rejection of those claims is reversed. The rejection of claims 1 and 4 is affirmed. Appellants filed no affidavit under Rule 204(c) showing a date of invention for claims 1 and 4 prior to Pfluger's 1966 filing date, In re Gemassmer, 51 CCPA 726, 319 F.2d 539, 138 USPQ 229 (1963), and have not antedated Pfluger as to those claims under 35 USC 119 and 120.

' That the final product temperature limitation is not material, as appellants argue, does not matter when the limitation is copied. Immateriality excuses only *failure* to copy a limitation of a patent claim. See Brailsford v. Lavet, 50 CCPA 1367, 318 F.2d 942, 138 USPQ 28 (1963); 37 CFR 1.205(a).

The New Matter Rejection

[10] The issue to be decided here is whether the limitation appearing in claim 6, carried forward into the other claims affected by this rejection, that the frozen foam be ground "to a particle size of at least 0.25 mm" before it is dried, was added to the instant application in violation of 35 USC 132. This new matter rejection rests on a finding by the PTO that the application as filed did not describe this limitation. Thus, the converse of what we said in In re Bowen, 492 F.2d 859, 864, 181 USPQ 48, 52 (CCPA 1974), is true in this case, namely, that this new matter rejection is tantamount to a rejection of the claims on the description requirement of 35 USC 112, first paragraph. The solicitor agrees with this.

We conclude that the originally filed specification clearly conveys to those of ordinary skill in the art that appellants invented processes in which the frozen foam is ground to a particle size of "at least 0.25 mm," and not, as the PTO asserts, only processes in which the particle sizes are no larger than 2 mm. See In re Smythe, supra.

The specification states, inter alia (emphasis ours):

> At the end of the [cooling] belt the extract is removed as a continuous rigid sheet which *may* then be broken up into fragments suitable for grinding. These fragments *may, for example,* be ground to a particle size which is *preferably* within the range 0.25 to 2.0 mm.
>
> * * *
>
> In a modification of the process, the frozen extract may be freeze-dried in the form of *plates or lumps* which are *subsequently* ground to the desired particle size.

The examples speak of drying frozen ground particles of sizes between 0.1 and 2 mm. While the specification indicates that the 0.25 to 2.0 mm range is preferred, we think it clearly indicates that, as an alternative embodiment of appellants' invention, the foam may be dried in lumps or plates of undisclosed size, which are reduced to the obviously smaller preferred particle size by grinding only *after* being dried. The solicitor argues that the claimed "range" has no upper limit, wherefore it is not disclosed. The clear implication of this disclosed modification is that appellants' specification does describe as their invention processes in which particle size is "at least 0.25 mm," without upper limit, as delineated by the rejected claims. The rejection of claims 6-10, 12-15, 17, and 26 under 35 USC 132 is reversed.

The "Non-Interference" Claims — 6-35 and 40-43

In the Examiner's Answer, appellants were granted the benefit of the filing date of their Swiss application for claims 16-25, 27-35, and 40-43. The examiner stated: "Claims 6-15 and 26, except for new matter, would otherwise be supported in the Swiss application." Our reversal of the new matter rejection eliminates the basis for the examiner's refusal to give claims 6-15 and 26 the benefit of appellants' Swiss filing date. Appellants' parent and Swiss applications contain the same disclosures concerning particle size as does the application on appeal, and we shall treat all the claims under this heading as entitled to the right of foreign priority claimed by appellants.

Our analysis of these claims will be broken down by the type of claim involved, i.e., process, apparatus, and product, and not as the board addressed them. In each discussion we will apply as prior art under §102(e) only those portions of the Pfluger patent disclosure that were carried forward from the Pfluger 1963 application (Pfluger 1963) through the two subsequent applications into the patent, as did the board. In re Lund, supra.

A. *Process Claims 6-14 and 16-29*

There are four independent process claims: claim 6, from which claims 7-14, 16, and 17 depend; claim 18; claim 19, from which claim 20 depends; and claim 21, from which claims 22-29 depend.

Pfluger 1963 contains the following disclosure, which, in substance, is carried forward into the patent:

> This invention is founded on the discovery that an aqueous aromatic liquid containing solids in suspension and solution may be dried without undergoing loss of aromatic volatiles by a process which comprises foaming the aqueous liquid to a substantial overrun while avoiding evaporation of said aqueous liquid, freezing said foam to below its eutectic point while avoiding evaporation of the aqueous liquid, subliming said aqueous liquid from the frozen foam to reduce the moisture of the foam to at least 10-20%, and further drying the foam to a stable moisture content.
>
> * * *

In many applications such foaming can be considerably increased by concentrating the solution or suspension to a relatively high solids content prior to incorporation of air or other gas such as nitrogen therein by first whipping and then freezing the foam, preferably by conductive freezing. During the foaming step, it is essential in order to prevent loss of volatiles to avoid any evaporative cooling of the material, i.e., evaporation of water during the foaming step. Also, during the freezing step evaporative cooling should be avoided. Other ways for creating a frozen foam without undergoing evaporative cooling involve the overt introduction to a solution or suspension of dry ice, i.e., solid carbon dioxide in a suitably ground or particulate form, whereby carbon dioxide gas is liberated upon subliming of the "dry ice" to cause foaming of the solution or suspension to occur. Similarly, refrigerated air or nitrogen can be introduced to the solution or suspension to cause freezing thereof incident to foaming the material. The foam preferably has a high overrun whereby the density of the solution or suspension is changed from above 1.0 gm./cc. to between 0.1-0.5 gms/cc.

Example I, the sole disclosed embodiment in which the foam density is given, shows foaming the extract to a density of 0.22 gm/cc.

Claims 19 and 20 recite a foam density of "between about 0.6 and about 0.8 gm/cc," outside the range disclosed by Pfluger 1963. The examiner's position was that Pfluger's disclosure of 0.5 gm/cc as an upper density limit suggests "about 0.6 gm/cc" as the lower limit in the processes of claims 19 and 20 "in the absence of a critical difference between them." We see no such suggestion. By preferring a high foam overrun, i.e., lower rather than higher foam densities, Pfluger 1963 teaches away from employing higher foam densities than its disclosed upper limit of 0.5 gm/cc. Appellants' "about 0.6 gm/cc" lower limit is sufficiently precise to describe foam densities above 0.5 gm/cc and thus outside the range of foam densities that persons of ordinary skill in the art would have been motivated to use by Pfluger 1963's disclosure of a preference for high overrun foams no denser than 0.5 gm/cc. The examiner's comment about the lack of a showing of a critical difference is based on his failure to appreciate that Pfluger 1963 teaches away from increasing foam density. The rejection of claims 19 and 20 under §103 is reversed.

[11] Claims 6-14, 16, 17, and 21-29 recite foam density ranges of "between about 0.4 and 0.8 gm/cc" and solids contents in the range of "about 25% to 60%." Claims 6-10, 12-14, 17, and 26 recite particle sizes of "at least 0.25 mm," claims 16 and 27 say "about 0.25 to 2 mm," claims 11 and 28 recite particle sizes "approximately equal to that of roast and ground coffee," and claims 21-25 do not mention particle size. Pfluger 1963's disclosed foam density range of 0.1-0.5 gm/cc covers values within the scope of all the above-listed claims; the solids contents disclosed in Pfluger 1963 Examples I (27%) and V (30%) are within the claimed ranges of 25-60%. Pfluger 1963 clearly teaches a process for making instant coffee comprising the steps of preparing and concentrating aqueous coffee extract, foaming the extract then freezing the foam, and drying the frozen foam, in that order. Pfluger 1963 teaches fragmenting the frozen foam into ¼-inch pieces before drying; ¼ inch is, of course, "at least 0.25 mm." Of course, the disclosure in the prior art of any value within a claimed range is an anticipation of the claimed range. We appreciate the arguments made in In re Malagari, 499 F.2d 1297, 182 USPQ 549 (CCPA 1974), and the discussion in In re Orfeo, 58 CCPA 1123, 440 F.2d 439, 169 USPQ 487 (1971), to the effect that ranges which overlap or lie inside ranges disclosed by the prior art may be patentable if the applicant can show criticality in the claimed range by evidence of unexpected results. The rejections here are under §103, not §102, which requires us to consider appellants' argument that their invention and Pfluger's disclosure are directed to different purposes and that persons of ordinary skill in the art would not look to Pfluger 1963 for a solution to the problem addressed by appellants. See In re Orfeo, supra.

[12] Appellants' contentions were thus stated in their main brief:

> The Board erred at the threshold in failing to appreciate that neither the Pfluger patent nor the 1963 Pfluger application gives any inkling or hint of the inventive concept underlying the rejected claims. * * * The Pfluger disclosures make no mention of product bulk density and contain no suggestion of altering or regulating that density in any manner. Neither does the reference suggest appellants' step of grinding the foam before freeze drying.
>
> * * *
>
> One of ordinary skill in the art reading the 1963 Pfluger disclosure would have no inkling of the problem addressed and solved by appellants; and one looking for ways to meet that problem would have no occasion to consider Pfluger or his expedients.

Without an antecedent basis for it in their application, appellants may not use this rationale to show unobviousness. In re Davies, 475 F.2d 667, 177 USPQ 381 (CCPA 1973). While appellants do disclose what the bulk density of their product "usually" is, we find no suggestion in appellants' application that their invention is addressed to the regulation of the bulk density of the product, and the claims make no express reference to such regulation. The only references in appellants' disclosure to this alleged problem and its solution which are apparent to us are (emphasis ours):

> After freeze-drying, the coffee extract is obtained in the form of a powder the density of which is *usually* 0.2 to 0.3 gm/cc.
>
> * * *
>
> Drying of the concentrated extract should *desirably* be carried out *under controlled conditions* such that the finished product possesses an appropriate *density* and colour. * * *
>
> * * * The conditions of freezing, notably belt speed, freezing temperature, thickness of foam layer as well as the *density of the foam*, are factors which have an important *influence* on the *colour* of the finished product and should therefore be carefully controlled.

The inadequacy of this disclosure is evident. There is no mention of *regulating* the final product density or of controlling solids content. We therefore see no basis for depreciating Pfluger as evidence of the scope and content of the prior art, as well as of the level of ordinary skill in this art, as appellants would have us do. Nor is there any factual basis for concluding that the ranges claimed by appellants are critical in themselves to their alleged inventive contribution.

[13] We find no error in the rejection under §103 of claims 6-14, 16, and 21-28, which recite no final product density. The only difference between claims 6, 12-14, and 16 and the Pfluger 1963 disclosure upon which appellants rely to show the unobviousness of the subject matter of the claims (and which does not relate to solids content or foam density) is the step of "grinding the frozen foam to a particle size of at least 0.25 mm" *prior* to freeze-drying.[8] Pfluger 1963, appellants assert, "fragments" the frozen foam prior to drying and "grinds" the foam only after it has been dried. As indicated above, the size of the fragments of frozen foam disclosed by Pfluger 1963 is "at least 0.25 mm." We do not think this difference shows the subject matter to be unobvious. Pfluger 1963 implies that the sizes of foam particles before and after drying are comparable; it would have been obvious to reduce the size of the foam particles by suitable mechanical means, whether it be called fragmenting or grinding, to the desired end product size before rather than after drying. Claim 11 differs only in its recitation of final product particle size, which Pfluger 1963 shows is an obvious matter of choice for those of ordinary skill in the art, who know how large ground roasted coffee bean particles are. The commercial motivation for making the particles this size is obvious. Appellants have not argued the patentability separately from claim 6 of claims 9 and 10, which add temperature and foam thickness limitations suggested by Pfluger and De George, as discussed infra in considering claims 24 and 25.

[14] Claim 8 likewise recites no final product density, but it requires that the freezing of the foam take place over a period of 7 to 25 minutes, which, appellants' application indicates, produces instant coffee "having a pleasant dark colour." Pfluger 1963 discloses freezing in liquid nitrogen or liquid air, which would be instantaneous, or rapid freezing on a belt, and states further, "The foam may be frozen at a high or a more gradual rate *without any apparent difference* in the utility thereof insofar as freeze drying is concerned * * *." (Emphasis ours.) Appellants have not shown that only their claimed freezing time produces coffee with a pleasant dark color. Thus, they have not overcome the prima facie case of obviousness made out by Pfluger 1963.

In light of appellants' concession in the amendment in which they added claims 37-39 that freeze concentration was known in the art, the rejection of claims 21-23, and 26-28 under Category VI, supra, becomes little more than a rejection on Pfluger 1963 alone. With the exception of freeze concentration, which is disclosed by the British patent, every element of claim 21 is disclosed by Pfluger 1963, as indicated supra. Appellants advance no arguments for the patentability of claim 21 different from those

[8] Appellants do not deny that the features added in claims 7, 12, 13, and 14 are taught in the art, and the record shows them to be known in the prior art.

we have already rejected for claim 6. Claim 22 adds only a recitation of the inert gases used in the foaming step, which were known in the prior art. Claims 26-28 recite the particle sizes of claims 6, 16, and 11, respectively; these particle sizes are not sufficient to show unobviousness for the reasons given supra. Claim 23, which was also rejected under Category VI, recites the freezing time of claim 8. It is unpatentable for the same reasons given for claim 8, supra.

Claims 24 and 25, to which Pfluger 1963, De George, and the British patent were applied under §103, call for the temperature and foam limitations already discussed under claims 9 and 10, supra. Temperature and foam thicknesses within the claimed ranges are disclosed by Pfluger 1963 in Example VI (freezing foam at —30°F. on a belt and subsequently loading foam onto trays to a 1-inch (approx. 25mm) depth for vacuum drying). Appellants do not allege that the ranges of claims 24 and 25 are critical.

[15] Claims 17, 18, and 29, on the other hand, recite the bulk density of the final product made by each process in positive terms. The board dismissed these final product density limitations as being merely recitations of the inherent result of observing the foam density and solids content ranges set forth in these claims. Although we found above that appellants' specification as filed does not disclose regulating product density by controlling the foam density and solids content in the process and that claims which failed to recite controlled product density could not rely on this feature to distinguish over the prior art under §103, these claims do require such regulation or control, by implication through their express recitation of the density of the final product to be obtained from the processes they delimit. That persons skilled in the art may not know how to ensure the claimed final product densities from the specification is pertinent only to a rejection on the enablement requirement of §112, first paragraph, which is not before us. The only question here is whether the subject matter of claims 17, 18, and 29, the scope of which is unquestionably clear, is obvious under §103.

[16] Pfluger 1963 discloses no final product densities and contains no teaching on how to achieve any particular final product density from practicing its process. The inherency of final product density adverted to by the board can be gleaned only from appellants' disclosure, if anywhere, which may not be used against them as prior art absent some admission that matter disclosed in the specification is in the prior art. In re Kuehl, 475 F.2d 658, 177 USPQ 250 (CCPA 1973); cf. In re Nomiya, 509 F.2d 566, 184 USPQ 607 (CCPA 1975). In the absence of disclosure of final product densities or how to achieve any desired density in the prior art applied by the PTO to claims 17, 18, and 29, we cannot say that the subject matter of these claims would have been obvious to persons of ordinary skill in the art.

The rejection of process claims 6-14, 16, and 21-28 is affirmed; the rejection of claims 17-20, and 29 is reversed.

B. *Apparatus Claims 30-35*

[17] The preamble of independent claim 30, carried forward into claims 31-35, recites that the apparatus is "for carrying out the process in claim 6." Appellants contend that this preamble gives "life and meaning" to the claims, serving to define the interrelationship of the mechanical elements recited in the body of the claims. This argument appears to be based on Kropa v. Robie, 38 CCPA 858, 187 F.2d 150, 88 USPQ 478 (1951), the classic case in this court on the construction of claim preambles. In Kropa the court surveyed prior cases and said 38 CCPA at 861, 187 F.2d at 152, 88 USPQ at 480-81:

> [I]t appears that the preamble has been denied the effect of a limitation where the claim or count was drawn to a structure and the portion of the claim following the preamble was a self-contained description of the structure not depending for completeness upon the introductory clause * * *. In those cases, the claim or count apart from the introductory clause completely defined the subject matter, and the preamble merely stated a purpose or intended use of that subject matter.

While we do not subscribe to the broad proposition that process limitations can never serve to distinguish the subject matter of apparatus claims from the prior art, we fail to see how the general process parameters of claim 6 require an arrangement of the apparatus means recited in claims 30-35 more specific than that set forth in the body of each claim. In no claim is the preamble relied on to provide an antecedent basis for terms in the body. See In re Higbee, 527 F.2d 1405, 188 USPQ 488 (CCPA 1976). The context of each invention is clear without reference to claim 6, unlike the situation in Kropa, supra, in which the preamble "An abrasive article" was the only portion of the claim defining the relationship of the components recited in the body of the claim; the court said, "The term calls forth a distinct relationship between

the proportions of grain and resin comprising the article." 38 CCPA at 862, 187 F.2d at 152, 88 USPQ at 481.

[18] Appellants do not argue the patentability of claims 32-35 separately from claim 30 and concede that Carpenter discloses the feature added in claim 31. We find that the teachings of Pfluger and De George (and Carpenter on claim 31) show that the subject matter of claims 30-35 would have been obvious to persons of ordinary skill in the art. These references are to be viewed for what they disclose in their entireties and not merely for their inventive contributions to the art. In re Ogiue, 517 F.2d 1382, 1387, 186 USPQ 227, 232 (CCPA 1975).

Pfluger 1963, in a portion carried forward to the patent, discloses the following:

> Advantageously, in following the teachings of the present process either in a vacuum freeze drying application or in an atmospheric freeze drying application, the frozen foamy mass may be arranged for either batch or continuous processing in any one of a variety of conventional plant handling applications. Thus, the foamy mass can be readily transferred from one food handling station to another, deposited in trays or continuous belts, superimposed on one another or otherwise conventionally located in the vicinity of the freeze drying influences. In the case of a typical freeze drying operation the foams may be frozen and deposited onto trays stacked one above the other on a suitable heat transfer surface in a vacuum chamber. In the case of an atmospheric freeze drying application the foams can be stacked one upon the other upon a foraminous drying member permitting the circulation of the drying medium, e.g. dry air, helium or nitrogen. Throughout all of such freeze drying applications it is imperative that the temperature of the foamy mass be maintained below the eutectic point of the material while drying to assure that the foam stays in a substantially solid or frozen state as distinguished from a melted or semi-liquid state, dehydration of the mass being achieved by a process of sublimation as distinguished from one of evaporation. Such conditions should be followed at least until the moisture content of the foamy mass has been substantially reduced to a point where it has lost at least a majority of its moisture and preferably is superficially dry to the touch, i.e. in the neighborhood of 10-20% moisture by weight.

Example VI of Pfluger 1963, which is carried forward as Example III of the Pfluger patent, shows heat controlling the vacuum chamber to assure a product temperature below —10°F. (De George teaches that the melting point of a 28% solids content extract is about 27°F., whereas the eutectic temperature is constant regardless of concentration at about —13.5°F.) De George discloses the use of endless belts, low speeds, and refrigerating means, and appellants, while arguing that De George treats the handling of solid slabs of frozen extract on refrigeration belts and not frozen foamed extracts, do not and cannot deny that De George discloses apparatus that persons of ordinary skill in the art would have deemed *suitable* for handling foams in the manner shown by Pfluger. Appellants also contend that neither reference discloses the "spreading device" recited in the claims, Pfluger 1963 showing only the application of 1/8 diameter ribbons of foam through a nozzle to stationary freeze drying trays. The reference in the portion of Pfluger 1963 quoted supra to the deposition of the foam on the belts is ample suggestion, in our opinion, that some means must be employed to apply the foamy mass to the continuous belts. The term "spreading device" is not defined in any special way by appellants and is broad enough to be the means for applying the foam to the belt suggested by Pfluger. The rejection of claims 30-35 is affirmed.

C. *Product Claims 15 and 40-43*

[19] These claims are cast in product-by-process form. Although appellants argue, successfully we have found, that the Pfluger 1963 disclosure does not suggest the control of bulk density afforded by appellants' process, the patentability of the *products* defined by the claims, rather than the processes for making them, is what we must gauge in light of the prior art. See In re Bridgeford, 53 CCPA 1182, 357 F.2d 679, 149 USPQ 55 (1966). Each of these claims defines a freeze-dried instant coffee product made by processes which, appellants have contended with respect to their process claims, produce, by virtue of the foam density and solids content ranges taught by appellants, products having a bulk density comparable to spray-dried instant coffee, i.e., 0.2-0.3 gm/cc as indicated in appellants' specification. The solids content and foam density ranges disclosed by Pfluger 1963 overlap those of appellants, and, it appears, the Pfluger process using solids contents and foam densities overlapping those of appellants will produce instant coffee which is indistinguishable from appellants' products. There is no evidence showing that Pfluger's product prepared, for example, using an extract of 30% solids con-

tent foamed to a density of 0.5 gm/cc differs from appellants' claimed products in any way, certainly not in any unobvious way. See In re Avery, 518 F.2d 1228, 1233-34, 186 USPQ 161, 165-66 (CCPA 1975). That *some* of the products *covered* by appellants' claims may not be disclosed or suggested by Pfluger 1963 is not relevant to patentability, since the claims embrace other subject matter completely disclosed by Pfluger 1963, complete disclosure in the prior art being the epitome of obviousness. In re Pearson, 494 F.2d 1399, 181 USPQ 641 (CCPA 1974). The rejection of these product claims under §103 on Pfluger* is affirmed.

Conclusion

The appeal is dismissed as to withdrawn claims 3, 5, 36, and 39. The decision of the board is affirmed as to claims 1, 4, 6-16, 21-28, 30-35, and 40-43, and is reversed as to claims 2, 17-20, 29, 37, and 38.

APPENDIX

2. The process of claim 1 wherein the extract is concentrated to between 35% and 60% soluble solids prior to the foaming step.

3. The process of claim 2 wherein the concentrated extract is foamed to an overrun density of between 0.1 to 0.7 gm/cc.

4. The process of claim 2 wherein the frozen foam is vacuum freeze-dried at a pressure of less than 500 microns and a final product temperature of less than 110°F.

5. The process of claim 3 wherein the frozen foam is vacuum freeze-dried at a pressure of less than 500 microns and a final product temperature of less than 110°C.

7. A process according to claim 6 in which said inert gas is at least one of the following gases, namely carbon dioxide, nitrous oxide and nitrogen

8. A process according to claim 6 in which the foam is frozen during 7 to 25 minutes.

9. A process according to claim 6 in which the foam is frozen on a moving belt which is cooled to a temperature between —12 and —70°C.

10. A process according to claim 6 wherein the foam is spread on the belt at a layer thickness of 10 to 40 mm.

11. A process according to claim 6 in which the frozen foam is ground, before freeze-drying, to a particle size approximately equal to that of roast and ground coffee.

12. A process according to claim 6 in which an aromatic condensate obtained by stripping roast and ground coffee is added to said concentrated extract before it is transformed into a foam.

13. A process according to claim 6 in which, after freeze-drying, the powdered coffee extract is aromatised by incorporation therein of 0.1 to 0.5% by weight of an aromatic condensate obtained by stripping of roast and ground coffee.

14. A process according to claim 13 in which said condensate is incorporated in said powdered extract in admixture with an oily carrier.

15. The coffee extract obtained by the process defined in claim 6.

16. Process according to claim 6 in which the frozen foam is ground to a particle size of about 0.25 to 2.0 mm.

17. Process according to claim 6 in which the freeze dried extract has a density of about 0.2 to 0.3 gm/cc.

18. Process for preparing a soluble coffee extract, which comprises adding inert gas to a concentrated aqueous extract of roast coffee having a solids content of about 25% to about 60% to provide a foam, freezing the foam to a solid mass, reducing the frozen foam to particles having a size of about 0.25 to 2.0 mm and freeze drying the frozen particles, the amount of inert gas added to the aqueous extract being sufficient to provide a freeze dried extract having a density between about 0.2 and 0.3 gm/cc.

19. Process for preparing a powdered coffee extract which comprises adding sufficient inert gas to a concentrated aqueous extract of roast coffee to provide a foam having a density between about 0.6 and about 0.8 gm/cc, freezing the foamed extract to a solid mass, grinding the frozen foam to an average particle size of 0.1 to 0.5 mm, freeze drying the ground particles to provide a finely powdered coffee extract, and agglomerating the finely powdered coffee extract.

20. Process according to claim 19, in which the powdered extract is agglomerated to provide an agglomerate having a density of about 0.2 to 0.3 gm/cc.

21. Process for preparing a powdered coffee extract which comprises increasing the soluble coffee solids content of an aqueous extract of roast ground coffee to about 25% — 60% by freeze concentration, separating the concentrated extract from ice crystals, adding an inert gas to the concentrated aqueous extract to provide a foam having a density between about 0.4 and 0.8 gm/cc, freezing the foam to a solid mass and freeze drying the frozen foam.

22. Process according to claim 21 in which the inert gas is selected from the group consisting of carbon dioxide, nitrous oxide and nitrogen.

23. Process according to claim 21 in which the foam is frozen during 7 to 25 minutes.

24. Process according to claim 21 in which the foam is frozen on a moving belt which is cooled to a temperature between —12 and —70°C.

25. Process according to claim 24 wherein the foam is spread on the belt at a layer thickness of 10 to 40 mm.

* Appellants argue in their reply brief that claims 40-43 "were never the subject of an accurate or proper rejection," because the examiner and the board incorrectly grouped them with other claims. As we have indicated, the rejection of claims 40-43 on Pfluger under §103 was "proper"; appellants do not contend that they could not understand the basis for the rejection because of failure of the PTO to give clear reasons for its action under 35 USC 132, and we find the explanations given by the examiner and board with respect to claims 40-43 to have been legally ample under §132. Cf. In re Gustafson, 51 CCPA 1358, 331 F.2d 905, 141 USPQ 585 (1964).

26. Process according to claim 21 in which the frozen foam is ground before freeze drying to a particle size of at least 0.25 mm.

27. Process according to claim 26 in which the frozen foam is ground to a particle size of about 0.25 to 2 mm.

28. Process according to claim 21 in which the frozen foam is ground before freeze drying to a particle size approximately equal to that of roast and ground coffee.

29. Process according to claim 21 in which the freeze dried extract has a density of about 0.2 - 0.3 gm/cc.

31. An apparatus according to claim 30 in which the means for cooling the belt includes a plurality of sprinklers disposed to spray the refrigerant onto the underside of the belt.

32. An apparatus according to claim 30 in which the belt comprises two sections each provided with separate cooling means, the first of said sections being cooled to a temperature of —12 to —29°C and the second section to —40 to —70°C.

33. An apparatus according to claim 30 also comprising means for fragmenting and milling the frozen foam.

34. An apparatus according to claim 30 in which the length of said belt is 15 to 25 metres and the driving means is adapted to move said belt at a linear speed of about 0.5 to 1.5 m/min.

35. An apparatus according to claim 30 in which said chamber is adapted to be maintained at a temperature of —25 to —45°C.

36. The process of claim 2 wherein the concentrated extract is foamed to an overrun density of between about 0.1 to 0.8 gm/cc.

37. The process of claim 2 wherein the concentrated (506) extract is foamed to an overrun density of between 0.4 to 0.8 gm/cc.

38. The process of claim 2 wherein the frozen foam is vacuum freeze-dried at a pressure of about 150 to 175 microns.

39. The process of claim 3 wherein the frozen foam is vacuum freeze-dried at a pressure of about 150 to 175 microns.

41. A coffee powder according to claim 40 wherein the extract before freeze drying contains about 25% to 60% by weight of soluble coffee solids.

42. A dry coffee powder having a density of about 0.2 to 0.3 gm/cc and comprising a freeze dried particulated foamed extract of roast and ground coffee, said extract containing before freeze drying up to about 60% by weight of soluble coffee solids.

43. A coffee powder according to claim 42 containing about 0.1% to 0.5% by weight of aromatic condensate obtained by stripping roast and ground coffee.

Baldwin, Judge, concurring in part and dissenting in part.

I agree with Judge Miller's treatment of claims 17-20 and 29. Otherwise, I join the majority opinion.

Miller, Judge, dissenting in part and concurring in part.

I dissent on claim 1. The error of the majority in affirming the rejection stems from a misstatement of the issue. It is not necessary when antedating a reference under 35 USC 102(a) or (e) to establish a prior reduction to practice, constructive or actual, of *all* the subject matter falling within the claims. It is necessary only to establish a reduction to practice of sufficient subject matter to render the claimed invention obvious to one of ordinary skill in the art. In re Spiller, 500 F.2d 1170, 182 USPQ 614 (CCPA 1974). The majority errs, therefore, in seeking a description in appellants' parent and foreign priority applications to support the entire claimed subject matter as though these were the applications in which the claims appear. See In re Ziegler, 52 CCPA 1473, 347 F.2d 642, 146 USPQ 76 (1965). Appellants have clearly shown possession of enough of the invention to antedate Pfluger 1966 by establishing a prior constructive reduction to practice in their parent and foreign applications of specific embodiments disclosing concentrating to 50% and 36% total solids and by a broader disclosure of "25 to 60%."

Although the rejection of claim 1 arises in the context of an attempt to initiate an interference, the rejection is clearly under 35 USC 102(a) or (e) and not under Rule 204(c), 37 CFR 1.204(c). Even if the rejection were under that rule, the substance of the rule's requirement for evidence sufficient to establish a prima facie case for a judgment of priority against Pfluger 1966 would be satisfied by the prior constructive reduction to practice of embodiments within claim 1 in appellants' parent and foreign applications. Hunt v. Treppschuh, 523 F.2d 1386, 187 USPQ 426 (CCPA 1975); Fontijn v. Okamoto, 518 F.2d 610, 186 USPQ 97 (CCPA 1975).

The majority cites In re Gemassmer, 51 CCPA 726, 319 F.2d 539, 138 USPQ 229 (1963), to support its decision on claim 1. It suffices to note that Gemassmer was decided more than a decade before In re Spiller, Hunt v. Treppschuh, and Fontijn v. Okamoto, supra.

I concur in the decision on claim 4 since appellants' parent and foreign applications are silent regarding final product temperature and a secondary heating step and, therefore, fail even as a constructive reduction to practice of the invention of claim 4.

I concur also in the decision on claims 19 and 20, but I do not find it necessary to hold, as the majority implicitly does, that "about 0.6" gm/cc excludes 0.5 gm/cc disclosed in the reference as the upper limit of merely a *preferred* range. Moreover, it is obvious from the reference that the process would work at a higher density than 0.5,

although inferior results might be expected. My concurrence rests on the requirement of claims 19 and 20 of a specific sequence of steps not suggested by the prior art, namely: providing a high density of about 0.6 to about 0.8 gm/cc, grinding to a fine particle size prior to freeze drying, freeze drying, and finally agglomerating the fine particles into larger particles. This achieves a "highly coloured product of regular particle size." There is no suggestion in the prior art of deliberately grinding to a fine size and then agglomerating to a larger size.

I dissent on claims 17, 18, and 29, because there is at least a prima facie relationship between product and foam densities. The board noted this by stating that "the freeze dried density of the coffee would be inherent in view of the same range of foam overrun density disclosed by Pfluger." Since the foam densities and other conditions disclosed by Pfluger for the process claimed are approximately the same, appellants should be required either to show that the reference does not achieve the same product densities or to establish criticality. Since they have not done so, I would affirm the rejection of claims 17, 18, and 29.

District Court, N. D. Illinois, E. Div.

Standard Pressed Steel Co.
v. Midwest Chrome Process Company

No. 74 C 2781 Decided July 29, 1976

TRADEMARKS

1. Court of Customs and Patent Appeals — Contrasted with R. S. 4915 suits (§28.10)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Court of Customs and Patent Appeals would have decided opposer's appeal on evidence produced before Trademark Trial and Appeal Board, but applicant's election to have all further proceedings conducted by way of civil action in federal district court altered procedure.

2. Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trial de novo (§59.25)

Revised Statues 4915 suits (35 U.S.C. 145) — Weight given decision being reviewed (§59.30)

15 U.S.C. 1071(b) proceedings are not strictly de novo; federal district court is not totally free to disregard all that happened before Trademark Trial and Appeal Board, although parties may present new evidence and enlarge pleadings; 15 U.S.C. 1071(b) alternative review procedures are designed to allow litigants to produce new evidence, but federal district court is not free to substitute its judgment on questions of fact, such as likelihood of confusion, unless new evidence is adduced that is sufficient to produce thorough conviction to contrary of board's decision.

3. Pleading and practice in courts — Motions — For summary judgment — In general (§53.6331)

Revised Statutes 4915 suits (35 U.S.C. 145) — Pleading and practice (§59.10)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trial de novo (§59.25)

Summary judgment in trademark cases can be granted on same principles as in other cases; distinguishing factor is that trademark cases, like patent and copyright cases, generally involve questions of fact that cannot be resolved in motion for summary judgment; it would not be improper to grant applicant's cross motion for partial summary judgment at time that would allegedly deprive opposer of its right to introduce new evidence in its federal district court action under 15 U.S.C. 1071(b), but it would be inappropriate to deny opportunity by granting motion, even if it appeared there was no genuine issue of material fact, if opposer needed additional time to conduct discovery and produce additional evidence; court will enter appropriate judgment if applicant can establish that there is no genuine issue of material fact remaining for trial and it is entitled to judgment as matter of law.

4. Identity and similarity — How determined — Considering goods (§67.4057)

Registration — Principal register (§67.753)

15 U.S.C. 1052(d) provides that no mark may be registered on principal register if it consists of mark that so resembles registered one, or mark or name previously used in United States and not abandoned, as to be likely to cause confusion, mistake, or to deceive when applied to applicant's goods; likelihood of confusion is determined by comparing goods identified in application with goods upon which opposer has established prior use of its pleaded mark or goods recited in opposer's pleaded registrations.

5. Identity and similarity — How determined — Side by side comparison (§67.4073)

Mere side-by-side comparison of marks is not likelihood of confusion test, so that other factors must be considered before making final conclusion on likelihood of confusion issue.

6. Pleading and practice in courts — Motions — For summary judgment — In general (§53.6331)

Revised Statutes 4915 suits (35 U.S.C. 145) — Pleading and practice (§59.10)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Revised Statutes 4915 suits (35 U.S.C. 145) — Weight given decision being reviewed (§59.30)

Identity and similarity — How determined — Purchasers and selling methods (§67.4071)

Likelihood of confusion decreases as customer market's sophistication increases; fact that there is sufficient evidence to support Trademark Trial and Appeal Board conclusion on nature of customer market and no evidence was proffered in 15 U.S.C. 1071(b) federal district court action to rebut it warrants conclusion that there is no genuine issue of material fact on question.

7. Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Evidence — Of confusion (§67.337)

Absence of actual confusion between parties that are not presently in direct competition does not advance applicant's position or damage opposer's in its 15 U.S.C. 1071(b) federal district court action for relief from Trademark Trial and Appeal Board decision.

8. Identity and similarity — How determined — Doubt against newcomer (§67.4067)

Latecomer has responsibility to avoid confusion.

9. Marks and names subject to ownership — Descriptive — In general (§67.5071)

Distinctive mark or name will be more broadly protected as trademark, but general words or names that have been applied to and used as trademarks for large number and variety of products will be protected only within range of use on similar goods; distinctive mark should be afforded broader protection.

10. Pleading and practice in Patent Office — In general (§67.671)

Ex parte issue is one relating to registrability of mark itself, in contrast to mark's eligibility for registration vis-a-vis other marks, that is, whether mark is eligible for registration in view of specific rights of other parties.

11. Revised Statutes 4915 suits (35 U.S.C. 145) — Issues determined (§59.05)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Federal district court, in opposer's 15 U.S.C. 1071(b) action for relief from Trademark Trial and Appeal Board decision, has authority to determine registrability of applicant's mark even when issues of registrability might be termed ex parte.

12. Pleading and practice in courts — Motions — For summary judgment — In general (§53.6331)

Revised Statutes 4915 suits (35 U.S.C. 145) — Trademarks (§59.20)

Acquisition of marks — Character and extent of use — In general (§67.0731)

Applications to register — In general (§67.131)

Applicant, to register mark, must state its first use in commerce; trademark on goods is considered to be used in commerce when it is placed on goods or their containers in any manner and goods are then sold or shipped in interstate commerce; minimal amount of commerce in terms of either sale or transportation will suffice, providing that transaction must not be sham, and there

mid and aqueous triethanolamine salt of DNBP). The four herbicidal formulations were applied to field plots having areas of 200 ft.^{2}. The plots were 10 ft. wide and 20 ft. long, and there were three replications for each treatment including three untreated check plots. The soil in the plots was prepared for seeding and soybeans were planted in all plots the first week in June. The herbicidal test formulations were applied broadcast over all foliage three weeks later. The soybeans and weeds had emerged and were growing actively. The plots were in a field having a heavy infestation of ragweed lambsquarters, and pigweed. Seven weeks later, the fresh weights of soybeans and weeds were measured on an area 3.3 ft. x 20 ft.—66 ft.^{2}—(two crop rows, 36" row spacing). The three untreated check plots averaged 8.5 lbs. of weeds, fresh weight and 24.2 lbs. soybeans. These average amounts were each assigned the unitary value 100, and the herbicide-treated plots were compared in terms of percentage of the untreated averages.

The results were as shown in the table:

Treatment and Rate in lbs. active ingredient per acre		Weeds	Soybeans
Check Plots		100 (8.5 lbs.)	100 (24.2 lbs.)
Diphenamid + DNBP + Chloroform	1.0 + 0.75	74%	88%
	2.0 + 1.5	38	74
	4.0 + 3.0	21	57
Diphenamid alone	1.0	69	96
	2.0	97	92
	4.0	73	92
DNBP alone (aqueous solution of triethanolamine salt-Preemerge®)	0.75	87	84
	1.5	61	78
	3.0	77	82
Diphenamid + DNBP (Tank mix of 50 W. Diphenamid and Preemerge®)	1.0 + 0.75	75	89
	2.0 + 1.5	58	83
	4.0 + 3.0	57	83

The examiner and board were of the view that the affidavit results are insufficient to overcome the prima facie case of obviousness established by the references, Vostral's conclusions and appellants' contentions to the contrary notwithstanding. We agree. As the board noted, the affidavit data shows that application of the appellants' herbicidal composition at a rate of 1.75 lbs./acre total active ingredient "gives results substantially identical * * *" to those obtained when the prior art "tank mix" composition is applied at that rate. Composition claims 1-5 and process claims 10-13 contain no limitation concerning the amount of Diphenamid and DNBP herbicidal ingredient in the composition or the amount of those active ingredients applied per acre in carrying out the process. The limitations appearing in composition claims 6-9 and process claim 14 pertaining to a ratio of Diphenamid to DNBP of 2:1.5 are of no avail to appellants either, for such compositions can readily be applied to weeds at a rate of 1.75 lbs. total active ingredient/acre, the rate at which the affidavit shows no nonobvious results are obtained. Clearly, appellants' objective evidence of nonobviousness is not commensurate in scope with claims 1-14 which the evidence is offered to support. See In re Tiffin, 58 CCPA 1420, 448 F.2d 791, 171 USPQ 294 (1971), modifying 58 CCPA 1277, 443 F.2d 394, 170 USPQ 88 (1971), and cases therein.

With respect to process claims 15 and 16, which do recite that 2.0 lbs. Diphenamid and 1.5 lbs. DNBP (or 4.0 and 3.0 lbs., respectively, in claim 16) are applied per acre, somewhat different considerations apply. Both the examiner and board observed that several references of record, not heretofore mentioned, indicate that chlorohydrocarbons are themselves herbicides, and that appellants have provided no data as to the per se herbicidal activity of the chlorohydrocarbon solvent which is utilized in the emulsifiable concentrate employed in appellants' process. While appellants deprecate those references as "ancient" history and the epitome of "primitiveness," it should be noted, as we pointed out earlier, that

a reference of relatively recent vintage—Lemin itself—discusses the "phytotoxic" effect of chlorohydrocarbon herbicide carriers. The record before us does not contain clear and convincing evidence that any increase in herbicidal activity shown by appellants' emulsifiable concentrate compositions when applied at rates of 3.5 and 7.0 lb./acre total active ingredient is not due at least in part to the presence of the chlorohydrocarbon solvent in that composition. We think that evidentiary defect is fatal to appellants' case. See, by way of analogy, In re Lemin, 56 CCPA 1050, 408 F.2d 1045, 161 USPQ 288 (1969).

The decision is *affirmed.*

Court of Customs and Patent Appeals

In re ANDERSON

No. 8837 Decided Jan. 26, 1973

PATENTS

1. Specification — Claims as disclosure (§62.3)

Unamended original claim in application is considered as part of original disclosure.

2. Specification — Sufficiency of disclosure (§62.7)

In determining what is disclosed, consideration cannot be restricted to major part of disclosure; applicant is entitled to have the whole of his disclosure considered.

3. Specification — Sufficiency of disclosure (§62.7)

First paragraph of 35 U.S.C. 112 does not require a specific example of everything within scope of broad claim; in application wherein there are specific examples of what appears to be preferred embodiment and best mode contemplated by applicant of carrying out claimed invention, and wherein court is dealing only with a possible alternative embodiment within scope of claims, claims cannot be limited to specific examples, where there is clear disclosure of a broader invention.

4. Specification — Sufficiency of disclosure (§62.7)

Where only essential characteristic of material disclosed is solubility and, although hemostatic embodiment is exemplified, it may or may not be hemostatic, fact that applicant states that he does not limit invention to this particular property does not compel him to give an example of a material lacking this characteristic on penalty of having to restrict claims to hemostatic material.

5. Claims — Broad or narrow — In general (§20.201)

Claims — Dependent (§20.35)

Dependent claims, which merely add a limitation to combination by calling for medication, are not too broad, since they are inherently limited to such medication as would be useful in the particular application; no one of ordinary skill in the art would use any other kind of medicament; court is dealing with combination claims, not with claims for medicaments per se; it is always possible to put something into a combination to render it inoperative; it is not function of claims to exclude all such matters but to point out what the combination is.

6. Amendments to patent application — New matter (§13.5)

In determining whether amendment to claim constituted new matter, question is not whether added word was a word used in specification as filed but whether there is support in specification for employment of word in claim, i.e., whether concept is present in original disclosure.

Particular patents—Dressing

Anderson, Wound Dressing, claims 1 to 6 and 8 of application allowed; claims 7, 9, and 10 refused.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Robert J. Anderson, Serial No. 642,294, filed May 31, 1967; Patent Office Group 120. From decision rejecting claims 1 to 10, applicant appeals. Affirmed as to claims 7, 9, and 10; reversed as to claims 1 to 6 and 8.

S. AUGUSTUS DEMMA, New York, N. Y., for appellant.

S. WM. COCHRAN (RAYMOND E. MARTIN of counsel) for Commissioner of Patents.

Before MARKEY, Chief Judge, and RICH, ALMOND, BALDWIN, and LANE, Associate Judges.

RICH, Judge.

This appeal is from the Patent Office Board of Appeals decision affirming the rejection of

claims 1-10, all claims of application serial No. 642,294, filed May 31, 1967, entitled "Wound Dressing." The application is stated to be a continuation-in-part of serial No. 337,709, filed January 8, 1964, which matured into patent No. 3,328,259, and of serial No. 782,515, filed December 23, 1958, now abandoned. We reverse in part and affirm in part.

The Invention

The invention described and claimed by appellant is a surgical dressing which is soluble in plasma and completely absorbable in the body and hence suitable for both external and internal use. It is intended to afford a substantial degree of containment against excess flow of plasma from a wound to which it is applied. Being absorbable, it becomes incorporated in the scab or eschar which forms over an external open lesion. The abstract forming part of the specification reads:

> The invention comprises a laminated dressing for a wound comprising a primary layer which is readily soluble in plasma and a secondary layer in face adhering contact with the primary layer, also soluble in plasma but to a lesser extent than the primary layer.

[1] Claim 1, which is the only independent claim and is an unamended original claim in this application and therefore, by elementary principles of patent law, to be considered as a part of the original disclosure,[1] reads (paragraphing supplied):

> 1. A laminated dressing for a wound comprising a laminated structure made up of two layers arranged face to face,
>
> both layers being plasma-soluble,
>
> one layer constituting a primary layer adapted to be applied directly to the wound, and being more readily soluble in plasma than the other layer,
>
> the other layer constituting a secondary layer serving as a backing for said primary layer.

It is thus seen that the invention of claim 1 is an article of manufacture comprising a combination of elements. Since claims 2-10 all depend, directly or indirectly, from claim 1, they are likewise combination claims. We shall not discuss them here but in connection with our discussion of the various rejections pertaining to them. The primary issue is the patentability of claim 1, the parent and broadest claim. We find it was erroneously rejected.

[1] Manual of Patent Examining Procedure 706.03(n) and 608.01(1), In re Oswald, 23 CCPA 1176, 83 F.2d 827, 29 USPQ 525 (1936), In re Myers, 56 CCPA 1129, 1138, 410 F.2d 420, 427, 161 USPQ 668, 673 (1969).

The Rejections

The board did not altogether agree with the grounds of rejections as stated by the examiner, affirmed some, reversed some, and added some of its own, not designated as new rejections. Appellant has made no issue of the fact that some of the rejections originated with the board. The Patent Office Solicitor has presented an analysis showing that we have seven different rejections before us, five of them on the ground that claims are "broader than warranted by the disclosure" for one reason or another. A sixth is for indefiniteness and the seventh for new matter.

We agree with the solicitor's explanation of what the statutory bases of these rejections *should* have been stated to be, which he has made in the light of two cases we decided after the date of the examiner's Answer herein and so close to the board's decision that it certainly did not consider them, In re Borkowski, 57 CCPA 946, 422 F.2d 904, 164 USPQ 642 (1970), and In re Wakefield, 57 CCPA 959, 422 F.2d 897, 164 USPQ 636 (1970). See also In re Hammack, 57 CCPA 1225, 427 F.2d 1378, 166 USPQ 204 (1970). The solicitor's explanation, which differs in several respects from the reasons given by the examiner and affirmed by the board, reads:

> It is apparent from the preceding analysis of the various grounds of rejection that all claims (grounds 1-5) have been rejected for failure to satisfy Section 112, paragraph 1, that claims 7, 9, and 10 have additionally been rejected for failure to satisfy Section 112, paragraph 2 (ground 6), and that claim 2 has additionally been rejected for failure to satisfy Section 132 (ground 7).

Further details as to these rejections will be given as we consider them. There is no rejection on pior art nor any prior art relied on.

Opinion

I

All claims except 4, 9 and 10[2] were rejected as "broader than warranted by the disclosure" in the use of the expression (in the third clause in claim 1 as set forth above) "a primary layer adapted to be applied directly to the wound, and being more readily soluble in plasma than the other layer."

In making this rejection, the examiner did not explain the basis of his assertion that the claims he so rejected are "broader than warranted by the disclosure." Challenged with having given no explanation, the only light he shed in his Answer was to say that "the above phrase was rejected on breadth," citing in justification In re Sus, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301 (1962), and In re Lund, 54 CCPA 1361, 376 F.2d 982, 153 USPQ 625 (1967). Of course, it was not the "phrase" the examiner was rejecting but the claim and we will assume that is what he meant. We find no support for the rejection in Sus. That case essentially involved the patentability of claims to a group of chemical compounds and to their uses claimed as processes of making printing plates. We found the claims to be not in compliance with § 112 because, as clearly stated at the end of the opinion, they did not conform to what the applicant *described* as his invention in the specification. The situation here is that the broad claims are of the same scope as the invention described. We also note that appellant relied on Sus [134 USPQ at 304] below for our statement, to which we adhere, that:

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions.

Lund was another case where the claims were for chemical compounds, useful as medicaments. It relied on Sus. We there said, "the *invention claimed* should be no broader than the *invention set forth* in the written description contained in the specification." We found that not to be the case. Here we find it is the case which is sufficient to distinguish Lund.

In affirming, the board presented an entirely different justification, as follows (emphasis ours):

> The *major part* of appellant's specification is directed to a laminate in which the primary layer is *hemostatic*. Such a layer is exemplified by the disclosures of two specific ethers of cellulose. The prophetic paragraph in page 5 of the specification, however, has no support by way of *exemplification* and does not demonstrate or suggest to one skilled in this art *how to use* any other material in the laminate. There is no suggestion as to any other specific materials which may be employed. Thus the examiner's rejection * * * is sustainable.

[2] It is quite true that the major part of appellant's specification is a disclosure of a primary layer having hemostatic properties but in determining what is disclosed we cannot restrict our consideration to the major part of the disclosure. Appellant is clearly entitled to have the whole of his disclosure considered. We have already adverted to the abstract and to original claim 1, both of which make clear that appellant did not regard his invention as limited to a hemostatic primary layer. His broad disclosures do not refer to the hemostatic property at all. Additionally, the "prophetic" paragraph referred to by the board appears to be the one which reads:

> Although the primary layer is described as being hemostatic, as far as certain aspects of the invention are concerned, it need not be so, as long as it is water-soluble or plasma-soluble, and can serve as a vehicle for medication, released upon dissolution in the plasma.

As we view it, the board's reason for agreeing that claim 1 is "broader than warranted by the disclosure" is not because the invention as disclosed is not of equal scope with claim 1 but because the claim is inclusive of a laminated dressing in which the primary layer is of non-hemostatic material *and* because there is (1) no "exemplification" of such a material and (2) no suggestion of "how to use" such a material in the laminate.

[3] On the first point, the tacitly assumed need for exemplification, we do not regard § 112, first paragraph, as requiring a specific example of everything *within the scope* of a broad claim. In re Gay, 50 CCPA 725, 309 F.2d 769, 135 USPQ 311 (1962). There is no question raised as to the fact that there are specific examples of what appears to be the preferred embodiment and best mode contemplated by the applicant of carrying out his claimed invention; we are here dealing only with a possible alternative embodiment within the scope of the claims. What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention This it may not do. As was stated in American Anode, Inc. v. Lee-Tex Rubber Products Corp., 136 F.2d 581, 585, 58 USPQ 7, 11 (7th Cir. 1943):

> There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1 [at pages 11 et seq.], 24 USPQ 26, 30 * * *

We consider the board's first reason insufficient.

On the "how to use" point we simply disagree with the board. In its broad aspect, appellant's dressing is a very simple thing. It has two layers of plasma-soluble material. The in-

[2] The examiner applied this rejection only to claims 1, 5, and 6. The board extended it to other claims by the statement: "This term, as appellant appears to recognize, appears in claims 1, 2, 3, 5, 6, 7 and 8." The fact is the "term" is a part of all claims.

ner layer, which lies against the wound, is, like the outer layer, soluble in plasma but dissolves more rapidly than the outer layer. There are various disclosed reasons for this. Because it dissolves, it does not have to be changed or removed; in dissolving it releases any medication it may be carrying; if it is of hemostatic material, in dissolving in the plasma it produces hemostasis. The backing layer, being more slowly soluble, acts to contain any excess plasma escaping through the primary layer, provides strength, and prolongs the useful life of the dressing. It will be understood that these two layers are adhered together and are in film or sheet form, it being disclosed that the primary or inner layer may be aerated in manufacture into porous or foam form. It is disclosed that making it porous increases the speed of its dissolution, as would be expected. We agree with appellant that the board erred in saying that the disclosure contains no suggestion of a material, which might be employed as the primary layer, which is non-hemostatic. Among the materials disclosed is methyl cellulose and the specification includes the statement:

> This compound, in dense form, has little or no hemostatic properties * * *.

[4] But even without this disclosure, we do not see why, in view of the clear disclosure, quoted above, that the primary layer need *not* be hemostatic, appellant should not have claims to his combination broad enough to include such materials even though no example thereof is given. According to the broad disclosure, the only essential characteristics of the primary layer are that it be plasma-soluble and more soluble than the backing. It may or may not be hemostatic. The hemostatic embodiment is exemplified. The mere fact that applicant has stated that he does not *limit* his invention to this particular property in the primary layer does not compel him to give an example of a material lacking this characteristic on penalty of having to restrict his claims to dressings in which the primary layer is hemostatic. In effect, all appellant is saying is that a hemostatic property in the primary layer is *not* part of the broad inventive concept he has disclosed and is claiming, though it may be an advantageous characteristic and is a limitation of some narrower claims and, probably, is the preferred form of the invention.

We will not, therefore, sustain this ground of rejection.

II

Claims 2 and 10 were rejected as "broader than warranted by the disclosure" because they use the term "medicament." The claims read:

> 2. A laminated dressing as described in claim 1, the primary layer carrying a medicament.
>
> 10. A laminated dressing as described in claim 9, said primary layer containing a medicament.

As to these claims the board expressly rejected the examiner's reasoning and substituted the following ground for sustaining the rejection:

> The criticized term [medicament], however, is too broad in that it includes medicaments not operative for appellant's stated purpose. It is well-known [sic] that "medicaments" include such materials as anti-coagulating agents and debriding agents, which would prevent the hemostatic action required of appellant's primary layer. This rejection will be sustained.

We have shown that the board erred in assuming that hemostatic action is required. The express disclosure is that it is not.

In the introductory portion of its opinion, the board said, "We will agree with appellant that he has adequately identified specific medicaments set forth in the examples [8 of them] of the patent, 3,328,259, maturing from the parent application." So we are not faced with inadequate disclosure of medicaments but merely with the proposition that because there *may* exist some medicaments *unsuited* to use in the dressing of this invention, the claims are too broad. The board is saying, in effect, that these claims which, being dependent, do no more than add a *limitation* to claim 1 (claim 9 from which claim 10 depends being itself dependent from claim 1) are too broad because not somehow limited to *operative* or suitable medicaments.

[5] The concept of medicament or medication involves a highly technical subject in an art requiring a high degree of technical skill—doctors of medicine and pharmacologists. It is common knowledge that some medicines of great utility are lethal when used in the wrong quantity, that one man's medicine is another man's poison, and that what is good medicine in one place may be bad medicine in another. The board, seemingly, is demanding a claim limitation to operative medicaments in operative quantity. We think that dependent claims such as the above, which merely add a limitation to the two-layer combination dressing by calling for medication in the primary layer, are inherently limited—by common sense if nothing else—to such medication as would be useful in the particular application. No one of ordinary skill in the art would use any other kind of medicament and there is no practical way to restrict the claim language so

as to exclude all inoperative or deleterious medicaments other than by the addition of such redundant terms as "suitable" or "operative for the purposes described." We dealt with similar arguments in In re Myers, 56 CCPA 1129, 410 F.2d 420, 161 USPQ 668, 672 (1969), and in dealing with an undue breadth rejection said:

> If every element in a mechanical combination claim were required to be so specific as to exclude materials known to be inoperative and which even those *not* skilled in the art would not try, the claims would fail to comply with 35 U.S.C. 112 [second paragraph] because they would be so detailed as to obscure, rather than [to] particularly point out and distinctly claim, the invention.

We are here dealing with combination claims, not with claims for medicaments per se. It is always possible to put something into a combination to render it inoperative. It is not the function of claims to *exclude* all such matters but to point out what the combination is.

We consider this ground of rejection unsound and will not sustain it.

III

Claim 3 reads:

> 3. A laminated dressing as described in claim 1, the primary layer containing a hemostatic agent.

The board said:

> We also agree with the examiner's position as to the term "a hemostatic agent" in claim 3 since, contrary to appellant's argument, the claim is not limited to such agents acting in a physical manner only but includes chemical agents, for example, those in styptic pencils, which also exhibit the stated function. This claim is obviously too broad.

The examiner merely indicated that "hemostatic agent" is too broad for some unspecified reason. The reasoning contributed by the board, apparently predicated on a theory that appellant's disclosure is limited to hemostatic agents acting in a "physical manner," seems to us without foundation. We have carefully studied the short application as well as the much more extensive patent issued to appellant on the parent application, part of which is incorporated into the application at bar by reference. One of the hemostatic materials is sodium carboxymethyl cellulose which, when plasticized, can be formed into a film to serve as the primary layer. Speaking of such a film the patent states:

> Tests have been conducted on simple cuts and it was found that the film would not only coagulate the blood, but would also combine with it, forming an artificial eschar which permitted healing thereunder.

We do not believe such coagulation of blood is a purely "physical" action. On the other hand, appellant disputes the board arguing that styptic pencils do not function through chemical action but by their astringent action which halts the flow of blood by contracting the tissues or blood vessels. We would hesitate to agree that this is not a "chemical" action. Whatever may be the shadowy line between physical and chemical behavior, we see no reason why appellant is not entitled to limit his main claim by specifying the presence in the primary layer of *any* hemostatic agent, of which he has disclosed several. He is no claiming such agents per se but is claiming a combination in which said agent is but one element. See In re Fuetterer, 50 CCPA 1453, 319 F.2d 259, 138 USPQ 217 (1963), and In re Boller, 51 CCPA 1484, 332 F.2d 382, 141 USPQ 740 (1964), which support appellant.

We will not sustain this ground of rejection.

IV

Claim 4 reads:

> 4. A laminated dressing as described in claim 1, the two layers constituting essentially cellulose derivatives.

Here again the examiner was just making an unexplained "breadth rejection." The board found "cellulose derivatives" clearly too broad because "inclusive of any and all derivatives, no matter how complex, produced in any manner, which are neither suggested by nor represented by the specific examples herein."

Once more we think the board was overlooking the fundamental fact that claim 4 is a limitation on claim 1, the two taken togethe being a claim to a combination of elemen constituting a dressing, not a claim to cellulose compounds per se. The board obviously goes too far in saying the term objected to is inclusive of all cellulose derivatives because it ignores the functional limitations in claim 1 which require that the two layers both be soluble in plasma and that the cellulose derivatives be such as can be formed into "layers" which can be laminated into a dressing. There is no question but that the class of cellulose derivatives has been sufficiently exemplified to provide an *enabling* disclosure.

We have considered the cases cited by the board to support its conclusion, In re Harwood, 55 CCPA 922, 390 F.2d 985, 156 USPQ 673 (1968), and Austenal Labs., Inc. v. Nobilium Processing Co. of Chicago, 153 F.Supp. 709, 115 USPQ 44 (DC ND Ill. 1957), but find them clearly distinguishable on their facts from the present case which we con-

sider to be governed by the principles announced in In re Metcalfe, 56 CCPA 1191, 410 F.2d 1378, 161 USPQ 789 (1969), and In re Fuetterer, supra.

We will not sustain this rejection.

V

Claims 7, 9, and 10 state that the backing layer contains a "cellulose derivative of the class consisting of methyl cellulose and hydroalkyl ether of cellulose." The issue here is a simple one: Is the term "hydro-alkyl" in this context "indefinite"?

The board held that "hydro-alkyl" is an "improper designation," "substantially meaningless," and not in conformity with standard chemical terminology. Appellant was trying to cover a disclosed compound identified in argument as *hydroxy* propyl cellulose.

Appellant comes very close to admitting that "hydro-alkyl" is a misnomer and it is quite apparent that the proper term would be "hydroxy-alkyl." Appellant says it should make no difference since those skilled in the art would know what was intended.

We agree that "hydro-alkyl" is clearly wrong. The term is not without meaning, however, and could be misleading. At the very least it renders the claims in which it appears indefinite.

We will sustain this rejection. Doing so, it becomes unnecessary to consider another rejection of claims 7, 9, and 10 on the ground that the same term renders the claims "broader than warranted by the disclosure."

VI

Claim 2 as originally filed reads:

> 2. A laminated dressing as described in claim 1, the primary layer *containing* a medicant. [Our emphasis.]

It was amended to change "containing" to "carrying" (see point II, supra) and on that account was rejected under 35 U.S.C. 132 as containing "new matter." The board said:

> We agree with the examiner's rejection of claim 2 apparently as based upon an amendment introducing new matter contrary to the requirements of 35 U.S.C. 132. There is no antecedent basis in the specification for the term "carrying." * * * This term, therefore, is not supported (35 U.S.C. 112) and has been improperly introduced into the claims.

It is true the term "carrying" does not appear in the specification in this connection. Neither does the term "containing," except as it appeared in original claim 2. The disclosure is that the primary layer may be "formulated with" medicaments and that that layer "can serve as a vehicle for medication, released upon dissolution in the plasma."

[6] The question, as we view it, is not whether "carrying" was a word *used* in the specification as filed but whether there is *support* in the specification for employment of the term in a claim; is the concept of carrying present in the original disclosure? We think it is. We think disclosure of the primary layer as a "vehicle" for the medication is quite sufficient for this purpose. If support for this conclusion be needed, we cite Webster's Seventh New Collegiate Dictionary (1963):

> *vehicle* * * * carriage, conveyance, fr. *vehere*
>
> to carry— * * * 1a: an inert medium in which a medicinally active agent is administered b: any of various other media acting usu. as solvents, carriers, or binders for active ingredients or pigments 2: an agent of transmission; CARRIER * * * 4: a means of carrying or transporting something; CONVEYANCE * * *

We will not sustain this rejection.

Conclusion

The rejection of claims 7, 9, and 10 is *affirmed*; the rejection of the remaining claims, 1-6, and 8 is *reversed*.

Court of Customs and Patent Appeals

In re OWNBY

No. 8850 Decided Jan. 26, 1973

PATENTS

1. Patentability — Anticipation — In general (§51.201)

Actual date when claimed invention was made is irrelevant, in view of statutory time bar of 35 U.S.C. 102(b), where cited patents issued more than one year before applicant's filing date.

2. Patentability — Anticipation — In general (§51.201)

Patentability — Invention — In general (§51.501)

Time frame for avoiding references that evidence obviousness (35 U.S.C. 103) is that imposed by section 102(b).

3. Patentability — Evidence of — Delay and failure of others to produce invention (§51.459)

Contention that claimed invention had long eluded those skilled in the art is not supported by evidence that an arrangement identical to applicant's has not been discovered in Patent Office files; more than this is needed to show unobviousness.

Particular patents—Electrical System

Ownby, Vehicle Electrical System, claims 1 to 5 and 8 to 10 of application refused.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Clifford H. Ownby, Serial No. 784,530, filed Dec. 2, 1968; Patent Office Group 212. From decision rejecting claims 1 to 5 and 8 to 10, applicant appeals. Affirmed.

B. R. PRAVEL, CLIFFORD H. OWNBY, and PRAVEL, WILSON & MATTHEWS, all of Houston, Tex., for appellant.

S. WM. COCHRAN (JERE W. SEARS of counsel) for Commissioner of Patents.

Before MARKEY, Chief Judge, and RICH, ALMOND, BALDWIN, and LANE, Associate Judges.

ALMOND, Judge.

This is an appeal from the decision of the Patent Office Board of Appeals affirming the rejection of claims 1-5 and 8-10 of appellant's application.[1] Claims 6 and 7 have been allowed. We affirm.

The invention relates to a vehicle electrical system having at least two batteries charged by a common generator. One of the batteries is used to start the vehicle engine and is usually referred to in the claims and specification as the "main battery." The other battery (or batteries) is used to power auxiliary systems and is usually referred to as the "auxiliary battery."

In one embodiment of the invention, a rectifier[2] is placed between the main battery and the generator so as to effectively isolate the main battery from the auxiliary battery while allowing the generator to charge both. Claim 9 is representative:

> 9. In an electrical system for a motor vehicle having a generator, a main battery and an auxiliary battery, wherein the main battery is connected to a starter motor for supplying electrical power for operating same, and wherein the main battery and the auxiliary battery are both connected to the vehicle generator, the improvement residing in:
>
> means including a solid state rectifier connected between said generator and said main battery for passing current to said main battery from said generator while blocking current flow in the opposite direction to thereby prevent the discharge of said main battery to electrical loads connected to said auxiliary battery.

The advantage of this arrangement is said to lie in the fact that the auxiliary battery can be used to power electrical accessories without discharging the main battery so that the latter's full output can be used for starting the vehicle.

In a second embodiment, one or more additional rectifiers are placed between the generator and all auxiliary batteries in order to isolate them from the main battery. Claim 1 is representative:

> 1. An automatic battery control system for vehicles and the like, comprising:
>
> (a) a first electrical circuit having a main battery for motor starting therein;
>
> (b) a second electrical circuit having an auxiliary battery therein;
>
> (c) a generator for charging both batteries;
>
> (d) a first rectifier connected in said first electrical circuit for permitting flow of electrical current in only the one direction from said generator to said main battery and for blocking current flow in the opposite direction; and
>
> (e) a second rectifier connected in said second electrical circuit for permitting flow of electrical current in only the one direction from said generator to said auxiliary battery and for blocking current flow in the opposite direction.

By so isolating both the main and auxiliary batteries, either can be discharged to power a specific electrical system without discharging the other.

Other claims call for additional limitations such as means for regulating the voltage output of the generator, a common terminal for connecting the generator to the rectifiers, etc.

Although the examiner made rejections under 35 U.S.C. 102 and 103, the board phrased its decision sustaining the examiner as follows:

> We have carefully reviewed the record herein, and as a result thereof, we find no reversible error in the examiner's holding that the subject matter of the claims on appeal is made obvious to one ordinarily skilled in the art by the prior art.

[1] Serial No. 784,530 filed December 2, 1968 as a continuation of application serial No. 532,299 filed March 7, 1966.

[2] The term "rectifier" is defined by appellant's specification as a device that permits current to flow in one direction while blocking flow in the reverse direction and includes diode rectifiers, transistors, solid state electronic devices, and other electrical devices adapted to permit the flow of electrical current in only one direction.

Clean copy of replacement for the paragraph in the specification beginning on page 13, line 27, and ending on page 14, line 7:

Two plasmids, termed pB28 and pB29, each with a mini-Tn3 transposon containing the chloramphenicol acetyltransferase (CAT) gene inserted into the *htrB* open reading frame at a different location. Nontypeable *Haemophilus influenza* strains 2019 B28 and 2019 B29 were deposited on November 14, 2000 with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 under the provisions of the Budapest Treaty, and all restrictions will be irrevocably removed upon the granting of a patent on this application. Strain B28 has been accorded accession number PTA-2667 and strain B29 has been accorded accession number PTA-2668. Each plasmid was used to transform nontypeable *H. influenzae* strain 2019 and bacterial cell transformants were selected for by growth in the presence of chloramphenicol (1.5 μg/ml), resulting in identification of mutant strains designated NTHi B28 and B29, respectively. Locations of the mTn3 insertion in the chromosomes of the NTHi mutants were confirmed by genomic Southern hybridization using the 2.4 kb *Bgl*II fragment as a probe. In particular, a *Bgl*II digest of NTHi strain 2019 DNA resulted in a 2.4 kb fragment; whereas similar digests of DNA from mutants NTHi B28 and B29 revealed 4.0 kb fragments. Further, the 4.0 kb fragments were digested by *Eco*RI which is present in the mTn3.

CLEAN VERSION OF THE PENDING CLAIMS

22-26, 29, and 32-34

22. (Amended) A method of making a mutant endotoxin comprising

mutating an *htrB* gene encoding a wild type endotoxin in a wild type gram-negative bacterial pathogen to provide the mutant endotoxin; wherein the mutant endotoxin is the same as the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A, and wherein the mutant endotoxin has substantially reduced toxicity when compared to the endotoxin of the wild type gram-negative bacterial pathogen.

23. A mutant endotoxin made according to the method of claim 22, wherein the mutant endotoxin was purified from the *htrB* mutant pathogen by phenol-water extraction or by protease digestion.

24. The mutant endotoxin according to claim 23, wherein the mutant endotoxin is conjugated to a carrier protein.

25. A mutant endotoxin made according to the method of claim 22.

26. The mutant endotoxin according to claim 25, wherein the mutant endotoxin is conjugated to a carrier protein.

29. (Amended) A method for producing endotoxin-specific antisera, the method comprising

(a) immunizing an individual with a vaccine formulation comprising an *htrB* mutant of a gram-negative bacterial pathogen, endotoxin isolated from the *htrB* mutant of the gram-negative bacterial pathogen, or endotoxin purified from the *htrB* mutant of the gram-negative bacterial pathogen wherein the endotoxin is conjugated to a carrier protein; and

(b) collecting antibody produced from the immunized individual;

wherein the *htrB* mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A.

32. The method of claim 22 wherein the gram-negative bacterial pathogen is of the genera *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella* or *Pseudomonas*.

33. The method of claim 29 wherein the gram-negative bacterial pathogen is of the genera *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella* or *Pseudomonas*.

34. (New) The method of claim 22, further comprising the step of purifying the mutant endotoxin.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Michael A. Apicella et al.

Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA

Docket No.: 875.001US2
Filed: October 13, 1998
Examiner: S. Devi

Serial No.: 09/077,572
Due Date: August 21, 2001
Group Art Unit: 1645

BOX AF
Commissioner for Patents
Washington, D.C. 20231

We are transmitting herewith the following attached items (as indicated with an "X"):

X A return postcard.
X Notice of Appeal (1 Page).
X Check for Notice of Appeal fee of $310.00.

Please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional required fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938, Minneapolis, MN 55402 (612-373-6900)

By: _____
Atty: Ann S. Viksnins
Reg. No. 37,748

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: BOX AF, Commissioner for Patents, Washington, D.C. 20231, on this 17th day of August, 2001.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael A. Apicella et al.	Examiner: S. Devi
Serial No.:	09/077,572	Group Art Unit: 1645
Filed:	October 13, 1998	Docket: 875.001US2
Title:	NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA	

REQUEST FOR REFUND

Commissioner for Patents
Washington, D.C. 20231

Applicants hereby request a refund of all fees required to be paid in connection with the Notice of Appeal filed August 17, 2001 and the Appeal Brief mailed herewith, in particular:

1. Notice of Appeal fee of $310.00 (see attached return postcard),
2. Appeal Brief filing fee of $320.00;
3. Request for Oral Argument fee of $280.00; and

A final Office Action was issued in this case on February 21, 2001, and Applicants filed their response on March 16, 2001, **within two months of the date of the final Office Action** (return postcard attached). As of August 17, 2001, just prior to the six-month date, Applicants had received neither an Advisory Action nor a Notice of Allowance, in spite of many telephone inquiries to the Examiner, her SPE, and other customer service representatives. This file has now been reported as lost.

Because of the Office's failure to take proper and timely action following receipt of Applicants' Amendment and Response to the final Office Action, Applicants were obliged to file a Notice of Appeal in order to keep this application pending. As of this date, the file is still reported to be lost, and Applicants have filed their Appeal Brief to keep from incurring further extension fees in the case.

It is believed that Applicants are entitled to a refund of all fees incurred by them after their Amendment and Response to Final Office Action was mailed on March 16, 2001, as listed above, and it is respectfully requested that a refund of said fees in the total amount of **$910.00** be credited to Deposit Account 19-0743.

Serial Number: 09/077,572
Filing Date: October 13, 1998
Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA

Please direct this communication to the Refund Section, Accounting Division, Office of Finance.

Respectfully submitted,

MICHAEL A. APICELLA ET AL.

By their Representatives,

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Date 15 October 2001 By _____

Ann S. Viksnins
Reg. No. 37,748

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